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Health and Environmental Effects Profile for Phthalic Acid Esters

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16. ABSTRACT

The Health and Environmental Effects Profile for Phthalic Acid Esters was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Di(2-ethylhexyl)phthalate has been evaluated as a carcinogen. The human carcinogen potency factor (q_1^*) for di(2-ethylhexyl)phthalate is 8.36×10^{-4} (mg/kg/day)$^{-1}$ for oral exposure.

Quantitative estimates have been presented provided sufficient data are available. Diethyl phthalate and di-n-butyl phthalate have been determined to be systemic toxicants. Reference Doses (RfD), defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effect during a lifetime, for diethyl phthalate and di-n-butyl phthalate are 0.75 and 0.13 mg/kg/day, respectively, for oral exposure. Existing data are insufficient to determine a Reference Dose (RfD) or a carcinogenic potency factor for diisononyl phthalate, dimethyl phthalate, di-n-octyl phthalate and n-butyl benzyl phthalate.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for di(2-ethylhexyl)phthalate, diethyl phthalate, di-n-butyl phthalate, dimethyl phthalate, di-n-octyl phthalate, n-butyl benzyl phthalate and diisononyl phthalate is 1000. Existing data are insufficient to determine an RQ value for di-n-heptyl phthalate.

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR PHTHALIC ACID ESTERS (PAEs)

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1985.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic exposures. An RfD (formerly known as the ADI) is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, RfDs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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EXECUTIVE SUMMARY

The literature was broadly searched for information pertaining to alkyl and aryl phthalate esters. The only compounds for which appropriate toxicological data were located include di(2-ethylhexyl)phthalate, diethyl phthalate, di-n-butyl phthalate, dimethyl phthalate, di-n-octyl phthalate, n-butylbenzyl phthalate and diisononyl phthalate.

Alkyl and aryl phthalates are generally colorless and odorless compounds (CEH, 1975). Most alkyl phthalates are liquids at ambient temperature. In general, the phthalate esters are poorly soluble in water but soluble in most organic solvents, including acetone, benzene and ether (Hawley, 1981). Phthalate plasticizers can undergo oxidation during plastic processing; antioxidants are added to resins to inhibit this reaction.

The alkyl and aryl phthalates are produced by reacting phthalic anhydride with an excess amount of the corresponding alcohol(s) in the presence of an esterification catalyst. The commercial products are usually $\geq$99% pure (U.S. EPA, 1978b). Sixteen U.S. manufacturers produce one or more of the 17 selected phthalic acid esters. Reported production figures and estimated production volumes were available for each of the alkyl phthalates. Total U.S. production volume of phthalic acid esters amounted to 1179 million pounds in 1984 (USITC, 1985). Alkyl and aryl phthalates are used predominantly as plasticizers for polyvinyl chloride resins (U.S. EPA, 1978a,b). To a lesser extent, they are used as plasticizers for other vinyl resins, cellulose ester plastics, synthetic elastomers and other polymers. End-uses include construction, home furnishing, consumer goods, packaging, electrical uses, transportation, medical products and others (U.S. EPA, 1978a,b). Some alkyl esters have minor applications as dielectric fluid [di(2-ethylhexyl)phthalate], active ingredients in pesticides, resin solvents, perfume fixatives, solvents and other uses (Hawley, 1981; U.S. EPA, 1979).

Hydrolysis is not expected to be a significant removal mechanism of phthalate esters (Suffet et al., 1981). Mabey et al. (1981) estimated that phthalate esters will not undergo significant oxidation in water. UV absorption spectra for some phthalates indicate that potential exists for direct photolysis in the environment. The photolysis half-life of n-butyl benzyl phthalate has been observed to be >100 days (Gledhill et al., 1980). Phthalate esters are reported to be metabolized in the aquatic environment by a variety of pure microorganisms and degraded by mixed microbial systems. The microbial degradation rates vary widely depending upon environmental conditions such as temperature, pH, amount of oxygen present and the phthalate structure (Hattori et al., 1975). Biodegradability of phthalates in freshwater decreases with increasing size and complexity of the phthalate ester chains (Hattori et al., 1975; Johnson et al., 1984).

Results from river die-away tests and activated sludge studies indicate that phthalates, as a class, undergo rapid degradation by bacteria commonly found in the environment (Saeger and Tucker, 1973a,b, 1976; Gledhill et al., 1980). For example, in a simulated lake microcosm Gledhill et al. (1980) observed >95% primary degradation of the complex ester n-butyl benzyl phthalate in 7 days. Under anaerobic conditions, biodegradation of short-chain alkyl esters has been shown to be possible, but slower than under aerobic conditions, while degradation of the long-chain esters has been shown to be very slight or undetectable (Johnson et al., 1984; Johnson and Lulves, 1975; Horowitz et al., 1982; Shelton et al., 1984). From the estimated Henry's Law Constants for n-butyl benzyl, di-n-butyl, di(2-ethylhexyl), diethyl, dimethyl and di-n-octyl phthalates, phthalate esters are predicted to not significantly volatilize from water (Lyman et al., 1982). Di-n-octyl phthalate may significantly volatilize from shallow rivers, although volatilization from deeper waters should not be significant (Lyman et al., 1982). In sea water, adsorption onto clay minerals and calcite appears to be a reversible process, whereas adsorption onto sediments is irreversible (Sullivan et al., 1982). This suggests that marine sediments may act as a final repository of phthalic acid esters (Sullivan et al., 1982). Calculated sediment-water partitioning coefficients indicate adsorption is likely for all phthalate esters, with adsorption tendency increasing with the size and complexity of the ester chain (Mabey et al., 1981). Complexation with the widely occurring humic and fulvic substances causes solubilization of phthalate esters in water, thus modifying their mobility (Matsuda and Schnitzer, 1971). Phthalates have been identified in living matter, and data collected from field and laboratory studies indicate that these compounds can bioaccumulate in aquatic organisms (Callahan et al., 1979a).

In air, the phthalate esters, as a class, are predicted to react with hydroxyl radicals, with a $t_{1/2}$ of <1 day (U.S. EPA, 1986a). The actual atmospheric $t_{1/2}$, however, may be longer than the estimated values because of adsorption onto airborne particulate matter. Removal of atmospheric phthalate by wet and dry deposition has also been observed (Kawamura and Kaplan, 1983; Atlas and Giam, 1981; Karasek et al., 1978; Weschler, 1984).

Significant hydrolysis of phthalate esters in wet soils is unlikely (Wolfe et al., 1980; Gledhill et al., 1980). Shanker et al. (1985) observed microbial degradation of di-n-butyl, di(2-ethylhexyl) and dimethyl phthalates in garden soil. Results indicate that soil microflora significantly degrade phthalates under aerobic conditions, and short-chain phthalates degrade at a faster rate than the longer chain phthalates. The anaerobic degradation of phthates was very slow compared with aerobic biodegradation.

The water solubilities and K_{ow} values of the phthalates suggest that adsorption to soils is dependent on the size and complexity of phthalate ester chains. Dimethyl phthalate should be reasonably mobile in soils, whereas large or branched chain esters, including diphenyl phthalate, should remain strongly adsorbed to soils. The mobility of phthalate esters in the presence of fulvic acid should increase. Since dimethyl phthalate is not likely to adsorb to soils, volatilization from dry soil surfaces may be a potential removal mechanism. Volatilization should be insignificant for other phthalates.

Phthalate esters are ubiquitous in the environment. They have been identified in surface waters in the United States and elsewhere in the world. The maximum reported concentration of di(2-ethylhexyl) phthalate in any surface water was 600 μg/ℓ, which was detected in Mississippi River water (Corcoran, 1973). The average concentration of individual phthalate esters in surface water is <1 μg/ℓ (Michael et al., 1984). Phthalate esters have also been identified in groundwater from contaminated sites; a maximum of 100 μg/ℓ of di(2-ethylhexyl) phthalate was detected in groundwater from a landfill site in New Castle County, DE (DeWalle and Chian, 1981). Several phthalate esters have been identified in drinking water abstracted both from surface water and groundwater. The maximum concentrations of diethyl, di-n-butyl, di(2-ethylhexyl) and butyl benzyl phthalates in 39 public water wells were reported to 4.6, 470, 170 and 38 μg/ℓ, respectively (CEQ, 1980; 1981; Burmaster, 1982). The Science Advisory Board of the U.S. EPA reviewed selected organic chemicals and estimated that the distribution of the phthalate esters is ~50% in U.S. drinking waters, with an overall phthalate concentration of ~1 μg/ℓ (U.S. EPA, 1978c). On the basis of these data and an average consumption rate of 2 ℓ/day, daily phthalate exposure to a U.S. individual from ingesting drinking water is estimated to be 2 μg.

Phthalate esters have been detected in ambient atmosphere. Probably the biggest contributor to atmospheric phthalate is the incineration of plastics that contain the esters (Peakall, 1975). The concentrations of di-n-butyl and di(2-ethylhexyl) phthalate in New York City's ambient air were 4.2 mg/m³ and 13.7 ng/m³, respectively (Bove et al., 1978). In College Station, TX, the corresponding values were reported to be 3.8 and 2.4 ng/m³ (Atlas and Giam, 1981). Until more air monitoring data become available, it is not possible to provide an average urban and rural levels of phthalate esters. Consequently, inhalation exposure of phthalate esters to the U.S. population residing in urban, suburban and rural areas cannot be estimated. Maximum exposure to phthalate esters is likely to occur under occupational conditions. Concentrations of phthalate esters ranged from 1.7-40 mg/m³ in a mixing area and from 10-66 mg/m³ in another area of a company manufacturing artificial leather and films of PVC (U.S. EPA, 1980b). NIOSH (1985) estimates that ~2,406,700 workers are annually exposed to diethyl, di-n-butyl and di(2-ethylhexyl) phthalate in the United States.

Several authors have identified phthalate esters in foods. Di(2-ethylhexyl) phthalate was detected at a concentration of 6.50 mg/kg in mackerel fillets (Musial et al., 1981). The concentration of di-n-butyl phthalate in rainbow trout from the Great Lakes was reported to be 8.1 mg/kg (Glass et al., 1977). In butter samples obtained from Japan, the concentration of di-n-butylphthalate was 4-11 mg/kg (Morita et al., 1973). Instant vegetable cream soup obtained from a Japanese market contained 6.35 mg/kg of di-n-butyl phthalate (Tomita et al., 1977). No estimate of phthalate ester exposure from food composites typically consumed by an individual in the United States is known.

Phthalate esters can be absorbed through the skin during the use of many cosmetic products, insect repellants and the water from PVC-lined swimming pools (U.S. EPA, 1980a). A special segment of the population is exposed to phthalate esters during medical/surgical procedures, such as hemodialysis and intravenous applications. No estimates on the dermal exposure of phthalate esters to individuals can be made from the data available in the literature.

It is difficult to draw conclusions about the relative toxicity of phthalic acid esters to aquatic biota because of the large variability in toxicity of each ester to different species. It is also difficult to pick out those species most sensitive to phthalates; however, Table 6-10 contains the most and least sensitive species and toxic concentrations reported for each ester. All of the esters listed in Table 6-10 caused toxic effects at $\leq$3.2 mg/ℓ. The lowest concentration reported to cause toxic effects was 0.003 mg/ℓ di(2-ethylhexyl) phthalate, which caused decreased production of offspring by Daphnia magna (Mayer and Sanders, 1973).

Although there were large differences in species sensitivity among major taxonomic groups, none of these groups except bacteria were especially more or less sensitive than other groups. Bacteria were clearly less sensitive than other organisms to di-n-butyl, diallyl, diethyl and dimethyl phthalates (Sugatt and Foote, 1981). The available information concerning freshwater and saltwater species indicated no difference in phthalate ester toxicity between freshwater and saltwater environments.

Many investigators have reported toxic effects of phthalates at concentrations greater than their aqueous solubility; however, the data indicate that all of the phthalates except dihexyl, dinonyl, di-n-decyl and diisodecyl phthlates were toxic to at least one species at concentrations near or below their solubility (Sugatt and Foote, 1981).

Information concerning residues of phthalic acid esters in aquatic biota suggests that accumulation is determined primarily by the degree to which species can metabolize and eliminate them (Soedergren, 1982). Fish generally have a well-developed mechanism in this regard and therefore do not accumulate phthalates to a great extent.

Oral studies show that di(2-ethylhexyl) phthalate, di-n-butyl phthalate, and diisooctyl phthalate are absorbed from the gastrointestinal tract (Williams and Blanchfield, 1974, 1975; Daniel and Bratt, 1974; Ikeda et al., 1978, 1980; Tanaka et al., 1978; Pollack et al., 1985a; Oishi and Hiraga, 1982; Teirlynck and Belpaire, 1985; Schmid and Schlatter, 1985). Pollack et al. (1985a) demonstrated that uptake of intraperitoneally administered di(2-ethylhexyl) phthalate into the blood is poor in rats. Orally administered phthalic acid esters are primarily and largely converted to their monoester derivatives by enzymes in the gastrointestinal tract before absorption (Albro and Thomas, 1973; Rowland, 1974; Rowland et al., 1977; Lake et al., 1977b; Carter et al., 1974; White et al., 1980; Pollack et al., 1985a; Teirlynck and Belpaire, 1985; Oishi and Hiroga, 1982). Other tissues such as the liver have also been shown to hydrolyze phthalic acid esters (Carter et al., 1974). In contrast, intraperitoneally administered di(2-ethylhexyl) phthalate is taken up primarily as di(2-ethylhexyl) phthalate, with only 1% hydrolyzed to monoethylhexyl phthalate (Pollack et al., 1985a).

Oral and intravenous studies indicate that di(2-ethylhexyl) phthalate, di-n-butyl phthalate and diisooctyl phthalate are not retained for long in the body (Tanaka et al., 1975, 1978; Williams and Blanchfield, 1974, 1975; Daniel and Bratt, 1974; Oishi and Hiraga, 1982; Teirlynck and Belpaire, 1985; Ikeda et al., 1978, 1980). In general, phthalic acid esters and metabolites distribute primarily to liver, kidneys, fat and the gastrointestinal tract. Metabolites have been found in almost every tissue; in particular a high concentration of monoethylhexyl phthalate, the hydrolytic derivative of di(2-ethylhexyl) pnthalate, has been observed in the testes of rats (Oishi and Hiraga, 1982). The distribution of di(2-ethylhexyl) phthalate and metabolites in various tissues, particularly liver, kidneys and fat, has been observed to vary with route of administration (diet, gavage, parenteral), vehicle and dose (Thomas and Thomas, 1984; Pollack et al., 1985a; Albro et al., 1982). In a dietary study on rats, radioactivity from ^{14}C-di(2-ethylhexyl) phthalate in the liver and fat declined with half-lives of 1-2 and 3-5 days, respectively (Daniel and Bratt, 1974). In gavage studies (Oishi and Hiraga, 1982), the disappearance of di(2-ethylhexyl) phthalate from tissues ($t_{1/2}$ ranging from 1.49-156 hours) was more rapid than for that of monoethylhexyl phthalate ($t_{1/2}$ ranging from 22.6-68 hours).

Although short-chain phthalic acid diesters such as dimethyl phthalate can be excreted unchanged in the urine, most phthalic acid diesters are further metabolized before excretion. The first step of metabolism entails hydrolysis of the parent compound to a monoester derivative. Once formed, the monoester derivative can then be further hydrolyzed to phthalic acid and excreted, conjugated with glucuronide then excreted, or oxidized and excreted. The first alternative occurs primarily with short-chain phthalic acid esters (Albro and Thomas, 1973; Albro and Moore, 1974; Albro et al., 1973). The second alternative is the primary route of metabolism for di(2-ethylhexyl) phthalate and occurs in all species except the rat (Albro et al., 1973, 1981, 1982; Kluwe, 1982a,b; Peck et al., 1978; Teirlynck and Belpaire, 1985; Schmid and Schlatter, 1985; Williams and Blanchfield, 1975; Daniel and Bratt, 1974; Chu et al., 1981; Tanaka et al., 1975; Thomas and Thomas, 1984); however, glucuronide conjugates of di-n-butyl phthalate have been observed in rats (Tanaka et al., 1978; Foster et al., 1982; Kaneshima et al., 1978). The third route of metabolism has been observed in rats, guinea pigs and hamsters (Williams and Blanchfield, 1974, 1975; Tanaka et al., 1978; Daniel and Bratt, 1974; Chu et al., 1981; Shuguenot et al., 1975). The metabolism of phthalic acid esters is not qualitatively affected by route of exposure (Kluwe, 1982).

Excretion of diisooctyl phthalate, di-n-butyl phthalate and di(2-ethylhexyl) phthalates has been studied (Ikeda et al., 1978, 1980; Schmid and Schlatter, 1985; Teirlynck and Belpaire, 1985; Williams and Blanchfield, 1974, 1975; Daniel and Bratt, 1974; Kaneshima et al., 1978; Tanaka et al., 1975, 1978). These compounds and their metabolites are excreted in urine, bile and feces; the relative importance of the route of excretion depends upon the compound and species, while the rate of excretion appears to be rapid. Half-lives of 7.9 and 12 hours were reported for urinary excretion of di(2-ethylhexyl) phthalate in humans and rats, respectively (Schmid and Shlatter, 1985; Teirlynck and Belpaire, 1985). Pharmacokinetic data on aryl or aryl/alkyl pthalates could not be located in the available literature as cited in the Appendix.

Di(2-ethylhexyl) and n-butyl benzyl phthalates have been tested for carcinogenic potential in feeding studies with F344 rats and B6C3F1 mice. Di(2-ethylhexyl) phthalate was found to cause increased incidences of liver neoplasms in both rats and mice (NTP, 1982b; Kluwe et al., 1982b). Using EPA's weight-of-evidence classification system, this is a group B2 chemical meaning there is sufficient evidence in animals and thus DEHP is probably carcinogenic in humans. n-Butyl benzyl phthalate caused an increase in myelomonocytic leukemia in female F344 rats (NTP, 1982a). Because of high background incidence of myelomonocytic leukemia in F344 rats and because dose-related and significant decreases in malignant lymphoma, all lymphoma, and leukemia or lymphoma were observed in male B6C3F1 mice (NTP, 1982a), there is only limited evidence to conclude that n-butyl benzyl phthalate is carcinogenic. The EPA weight of evidence category is group C, meaning that the compound is considered a possible human carcinogen.

The mutagenicity and genotoxicity of phthalic acid esters have been reviewed by Thomas and Thomas (1984) and Hopkins (1983). Di(2-ethylhexyl) phthalate and metabolites have yielded mostly negative results in Ames tests with _S_. _typhimurium_, and mixed results with _in vitro_ and _in vivo_ tests of genotoxicity. Diethyl phthalate, dimethyl phthalate, and di-n-butyl phthalate were found to be mutagenic in _in vitro_ microbial assays with _S_. _typhimurium_ (Kozumbo et al., 1982; Rubin et al., 1979; Seed, 1982).

Oral studies have shown that di(2-ethylhexyl) phthalate, di-n-butyl phthalate, and di-n-heptyl phthalate can produce adverse effects upon the developing fetus when mice and rats are exposed during gestation (Wolkowski-Tyl, 1984a,b; Bell et al., 1979; Bell, 1980; Shiota and Mima, 1985; Shiota and Nishimura, 1982; Shiota et al., 1980; Nakamura et al., 1979; Yagi et al., 1978, 1980; Tomita et al., 1982b; Onda et al., 1974). Whether the observed effects (reduced fetal weight, fetal mortality, gross external and skeletal malformations) represent a primary effect of the compound in question or whether they occur as a result of maternal toxicity has yet to be demonstrated unequivocally. Studies conducted by NTP (Wolkowski-Tyl et al., 1984a,b) indicate that mice are more sensitive than rats.

NTP has recently conducted reproduction and fertility assessments on CD-1 mice for diethyl phthalate (Reel et al., 1984) and di-n-octyl phthalate (Gulati et al., 1985). Dietary di-n-octyl phthalate had no effects on reproduction and fertility among parental or F_1 mice. Dietary diethyl phthalate had no effects on reproduction and fertility in parental mice, but diethyl phthalate-exposed F_1 mice had fewer pups/litter than did controls, as well as increased liver weights (males and females), increased prostate weights, increased pituitary weights (females only) and decreased sperm concentrations. Booth et al. (1983) and Plasterer et al. (1985) reported that dimethyl phthalate had no effects on reproduction in CD-1 mice. Dimethyl phthalate was administered by gavage on days 7-15 of gestation. The fertility of Sherman rats was not affected by dietary administration of di(2-ethylhexyl) phthalate (up to 0.4%) for 1-2 years (Carpenter et al., 1953).

Orally administered di(2-ethylhexyl), di-n-butyl, n-butyl benzyl, di-n-pentyl, diisobutyl and di-n-heptyl phthalates have been shown to cause testicular atrophy in rats to mice (Gray et al., 1977, 1982; Shaffer et al., 1945; Gangolli, 1982; Oishi and Hiraga, 1980a, 1983; Gray and Butterworth, 1980; Mangham et al., 1981; Oishi, 1985; Agarwal et al., 1985; Foster et al., 1980). Di-n-octyl, dimethyl, diethyl, dipropyl and di-n-heptyl phthalates did not cause testicular atrophy in rats (Gray and Butterworth, 1980; Foster et al., 1980). Species differences in phthalic acid ester-promoted testicular atrophy have been observed. Gray et al. (1982) failed to observe testicular atrophy in hamsters gavaged with di-n-butyl, di-(2-ethylhexyl) and di-n-pentyl phthalates at doses equimolar to those that caused atrophy in rats. In the same study, mice gavaged with equimolar doses of di-n-butyl, di(2-ethylhexyl) and di-n-pentyl phthalates had only slight focal atrophy.

Chronic or subchronic oral studies have been conducted with di(2-ethylhexyl), di-n-butyl, dimethyl, diisononyl, n-butyl benzyl and di-n-octyl phthalates (Carpenter et al., 1953; Harris et al., 1955; Nikonorow et al., 1973; Gray et al., 1977; Gangolli, 1982; NTP, 1982a,b; Kluwe et al., 1982b; Shaffer et al., 1945; Popp et al., 1985; Ganning et al., 1985; Nagasaki et al., 1974; Ota et al., 1974; Lake et al., 1976, 1977a; Maslenko, 1968; Food Research Laboratories, 1955; Brown et al., 1978; Smith, 1953; Lefaux, 1968; Piekacz, 1971; LeBreton, n.d.; Bornmann et al., 1956; Lehman, 1955; Livingston, 1971; Monsanto, 1972; Piekacz, 1971). Liver, kidneys and testes appear to be target organs. Occupational exposure to phthalate esters has been associated wih polyneuropathy (Milkov et al., 1973; Gilioli et al., 1978).

Acute oral LD_{50}s have been reported for di(2-ethylhexyl), dimethyl, di-n-butyl, diethyl, n-butyl benzyl, di-n-octyl, dihexyl, dinonyl and didecyl phthalates. These values are summarized in Table 5-11.

An interim q_1* of 8.36×10^{-3} $(mg/kg/day)^{-1}$ was derived for di(2-ethylhexyl) phthalate based on the incidence of hepatocellular carcinoma or adenoma in male mice in the NTP (1982b) study. This value is considered interim pending additional analysis of potential interspecies differences in metabolism. The concentrations in water associated with risk levels of 10^{-5}, 10^{-6} and 10^{-7} are 4.19×10^{-2}, 4.19×10^{-3} and 4.19×10^{-4} mg/ℓ, assuming that a 70 kg human consumes 2 ℓ/day. Additional metabolic factors need to be considered before a value is proposed.

The RfD of 0.75 mg/kg/day (52.5 mg/day) was derived for diethyl phthalate, based on a subchronic oral rat NOEL of 159 mg/kg/day in the study by Brown et al. (1978) and using an uncertainty factor of 1000. An RfD of 0.13 mg/kg/day (8.75 mg/day) for di-n-butyl phthalate is derived based on a 52-week oral rat NOAEL of 125 mg/kg/day in the study by Smith (1953) and using an uncertainty factor of 1000. The U.S. EPA (1980b) derived an RfD of

10 mg/kg/day (700 mg/day) for dimethyl phthalate based on a chronic rat NOAEL of 1000 mg/kg/day in the study by Lehman (1955) using an uncertainty factor of 100. A reevaluation of the Lehman (1955) study suggests that the data, as presented in this paper are inadequate for development of an RfD.

An RfD was not derived for di-n-octyl phthalate based on inadequate data. An RfD of 0.16 mg/kg/day (11.1 mg/day) could be derived for n-butyl benzyl phthalate based on a subchronic rat NOEL of 159 mg/kg/day in the NTP (1985) study. However, this RfD would not be protective for potential carcinogenic effects of butyl benzyl phthalate.

CSs were calculated for di(2-ethylhexyl) phthalate, diethyl phthalate, di-n-butyl phthalate, dimethyl phthalate, di-n-octyl phthalate, n-butyl benzyl phthalate and diisononyl phthalate (Table 9-7). In each case, the data that resulted in the highest CS, are recommended as the basis for the RQs (Tables 9-8 to 9-14). The RQ for each of the phthalate esters listed are >1000. Data were not sufficient for deriving an RQ for the other phthalate esters discussed in this document.

An F factor of 5.14×10^{-2} $(\text{mg/kg/day})^{-1}$ was calculated for di(2-ethylhexyl) phthalate, placing this chemical in Potency Group 3. Because the evidence for carcinogenicity in animals was sufficient, di(2-ethylhexyl) phthalate is placed in EPA Group B2. An EPA Group B2 chemical in Potency Group 3 has a low hazard ranking under CERCLA. The evidence for carcinogenicity of n-butyl benzyl phthalate in the NTP (1982a) study was limited, implying an EPA Group C classification, possible human carcinogen, while no data regarding the carcinogenicity of other phthalate esters were available; therefore, these chemicals are placed in EPA Group D.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AP	Acid phosphatase
AUC	Area under curve
BBP	n-Butyl benzyl phthalate
BCF	Bioconcentration factor
BOD	Biological oxygen demand
bw	Body weight
CAS	Chemical Abstract Service
CHO	Chinese hamster ovary
CS	Composite score
DAP	Diallyl phthalate
DBP	Di-n-butyl phthalate
DEHP	Di(2-ethylhexyl) phthalate
DEP	Diethyl phthalate
DHP	Dihexyl phthalate
DHeP	Diheptyl phthalate
DIBP	Diisobutyl phthalate
DIDP (DiDP)	Diisodecyl phthalate
DINP	Diisononyl phthalate
DIOP (DiOP)	Diisooctyl phthalate
DMP	Dimethyl phthalate
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DNP	Dinonyl phthalate
DOP	Di-n-octyl phthalate
DPep	Di-n-pentyl phthalate

LIST OF ABBREVIATIONS (cont.)

DUP	Diundecyl phthalate
EC_{50}	Concentration effective to 50% of recipients
FEL	Frank-effect level
K_{oc}	Soil sorption coefficient
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
MEHP	Monoethylhexyl phthalate
MTD	Maximum tolerated dose
NOAEL	No-observed-adverse-effect level
NOEC	No-observed-effect concentration
NOEL	No-observed-effect level
ppm	Parts per million
ppt	Parts per thousand
PVC	Polyvinyl chloride
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
SCE	Sister chromatid exchange
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SS	Saturated solution
TWA	Time-weighted average
UV	Ultraviolet
WS	Water solubility

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

The synonyms, CAS number, structure, empirical formula and molecular weight for each of the phthalic acid alkyl and aryl esters discussed in this report are presented in Table 1-1.

1.2. CHEMICAL AND PHYSICAL PROPERTIES

Alkyl and aryl phthalates are generally colorless and substantially odorless compounds (CEH, 1975). Most alkyl phthalates are liquids at ambient temperature. In general, the phthalate esters are poorly soluble in water but soluble in most organic solvents including acetone, benzene and ether (Hawley, 1981).

Alkyl phthalates undergo the typical reactions of carboxylic esters, for example, saponification by strong bases, hydrolysis in the presence of strong aqueous acids, reduction to alcohols by the action of hydrogen, ester interchange and conversion to amides by reaction with ammonia.

Commercially, phthalate plasticizers can undergo oxidation during plastics processing, forming peroxides which later decompose with development of colored and odorous compounds. Antioxidants such as bisphenol A are added to the resin to inhibit this reaction (U.S. EPA, 1978b).

Selected physical properties of a few phthalate esters are listed in Table 1-2. The data on the physical properties of phthalate esters varies to a great extent from one source to another. The most recent and apparently reasonable values for these parameters are given.

1.3. PRODUCTION DATA

Alkyl and aryl phthalates are formed by reacting phthalic anhydride with an excess amount of the corresponding alcohol(s) in the presence of an esterification catalyst (for example, sulfuric acid or p-toluenesulfonic

TABLE 1-1

General Information on Selected Dialkyl Phthalates

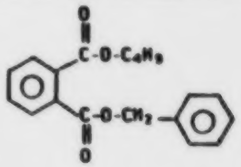
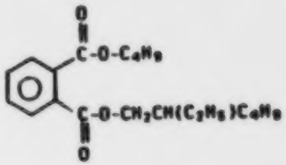
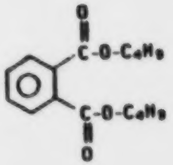
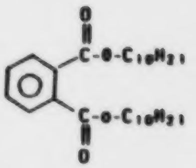
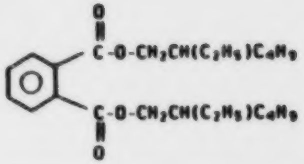
CAS Number	Chemical Name	Synonyms*	Chemical Formula	Molecular Weight	Structure
85-68-7	n-Butyl benzyl phthalate	1,2-benzenedicarboxylic acid, butyl phenylmethyl ester; BBP; benzyl n-butyl phthalate	$C_{19}H_{20}O_4$	312.37	
85-69-8	n-Butyl 2-ethylhexyl phthalate	1,2-benzenedicarboxylic acid, butyl 2-ethylhexyl ester	$C_{20}H_{30}O_4$	334.50	
84-74-2	Di-n-butyl phthalate	1,2-benzenedicarboxylic acid, dibutyl ester; DBP; n-butyl phthalate	$C_{16}H_{22}O_4$	278.35	
84-77-5	Di-n-decylphthalate	1,2-benzenedicarboxylic acid, didecyl ester; DDP; decyl phthalate	$C_{28}H_{46}O_4$	430.62	
117-81-7	Di(2-ethylhexyl) phthalate	1,2-benzenedicarboxylic acid, bis(2-ethyl hexyl) ester; DEHP; DOP; dioctyl phthalate; octyl phthalate	$C_{24}H_{38}O_4$	390.57	

TABLE 1-1 (cont.)

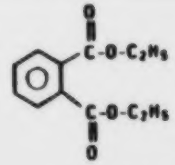
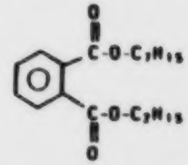
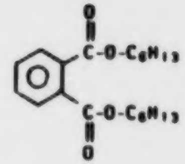
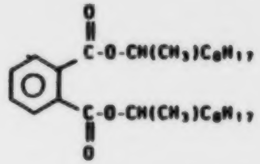
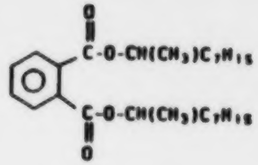
CAS Number	Chemical Name	Synonyms*	Chemical Formula	Molecular Weight	Structure
84-66-2	Diethyl phthalate	1,2-benzenedicarboxylic acid, diethyl ester; DEP; diethyl-o-phenylene-diacetates	$C_{12}H_{14}O_4$	222.23	 O C-O-C₂H₅ C-O-C₂H₅ O
3648-21-3	Diheptyl phthalate	1,2-benzenedicarboxylic acid, diheptyl ester; heptyl phthalate; DHeP	$C_{23}H_{34}O_4$	362.56	 O C-O-C₇H₁₅ C-O-C₇H₁₅ O
84-75-3	Dihexyl phthalate	1,2-benzenedicarboxylic acid, dihexyl ester; DHP	$C_{20}H_{30}O_4$	334.50	 O C-O-C₆H₁₃ C-O-C₆H₁₃ O
26761-40-0	Diisodecyl phthalate	1,2-benzenedicarboxylic acid, diisodecylester; DIDP	$C_{28}H_{46}O_4$	446.68	 O C-O-CH(CH₃)C₈H₁₇ C-O-CH(CH₃)C₈H₁₇ O
28553-12-3	Diisononyl phthalate	1,2-benzenedicarboxylic acid, diisononylester; DINP	$C_{26}H_{42}O_4$	418.68	 O C-O-CH(CH₃)C₇H₁₅ C-O-CH(CH₃)C₇H₁₅ O

TABLE 1-1 (cont.)

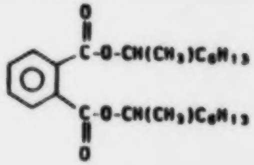
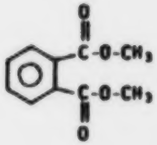
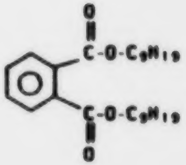
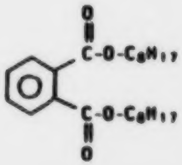
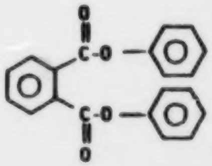
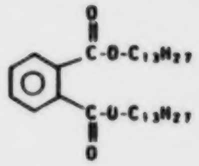
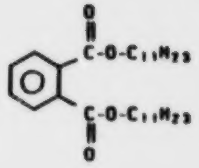
CAS Number	Chemical Name	Synonyms*	Chemical Formula	Molecular Weight	Structure
27554-26-3	Diisooctyl phthalate	1,2-benzenedicarboxylic acid; DIOP	$C_{24}H_{38}O_4$	390.62	
131-11-3	Dimethyl phthalate	1,2-benzenedicarboxylic acid, dimethyl ester; DMP	$C_{10}H_{10}O_4$	194.19	
84-76-4	Dinonyl phthalate	1,2-benzenedicarboxylic acid, dinonyl ester; DNP	$C_{26}H_{42}O_4$	418.68	
117-84-0	Di-n-octyl phthalate	1,2-benzenedicarboxylic acid, di-n-octyl ester; DOP; DNOP; n-octyl phthalate	$C_{24}H_{38}O_4$	390.62	
84-62-8	Diphenyl phthalate	1,2-benzenedicarboxylic acid, diphenyl ester; DPP; phenylphthalate	$C_{20}H_{14}O_4$	318.33	

TABLE 1-1 (cont.)

CAS Number	Chemical Name	Synonyms*	Chemical Formula	Molecular Weight	Structure
2119-06-2	Ditridecyl phthalate	1,2-benzenedicarboxylic acid, ditridecylester; DTDP	$C_{34}H_{59}O_4$	530.92	
3648-20-2	Diundecyl phthalate	1,2-benzenedicarboxylic acid, diundecyl ester; DUP	$C_{30}H_{50}O_4$	474.80	

*SANSS, 19[illegible]

TABLE 1-2

Chemical and Physical Properties[a]

CAS Number	Chemical Name	Melting Point (°C)	Boiling Point (°C)	Vapor Pressure	Water Solubility	Log K_{ow}	Specific Gravity	Refractive Index
85-68-7	n-Butyl benzyl phthalate	-35	370	$8.6x10^{-6}$ mm Hg (20°)	2.9 mg/ℓ	4.91	1.113-1.121 (25/25°C)	1.535-1.540 (25°)
85-69-8	n-Butyl 2-ethyl-hexyl phthalate	-37[b]	224 (5 mm Hg)	NA	NA	7.61	0.9941 (25°C)	1.4868 (25°C)
84-74-2	Di-n-butyl phthalate	-40	335	$1.06x10^{-5}$ mm Hg (25°C)	13 mg/ℓ (25°C)	4.72	1.047 (20/4°C)	1.4915 (25°C)
84-77-5	Di-n-decyl phthalate	-37[c]	261 (5 mm Hg)	NA	0.33 mg/ℓ[c] (24°C)	NA	0.9675 (20/20°C)	NA
117-81-7	Di(2-ethyl-hexyl) phthalate	-46[b]	236 (5 mm Hg)	$0.62x10^{-7}$ mm Hg (25°C)	0.29 mg/ℓ (20°C) 0.40 mg/ℓ (25°C)	9.64	0.986 (20/20°C)	1.4830-1.4859 (20°C)
84-66-2	Diethyl phthalate	-40.5	296	$3.45x10^{-3}$ mm Hg (20°C)	129 mg/ℓ (20°C) 896 mg/ℓ (25°C)	2.47	1.123 (25/4°C)	1.5002 (25°C)
3648-21-3	Diheptyl phthalate	NA	NA	NA	NA	NA	NA	NA
84-75-3	Di-n-hexyl phthalate	-33[b]	210 (5 mm Hg)	NA	NA	7.74	1.008 (20°C)	1.491 (20°C)
26761-40-0	Diisodecyl phthalate	-50[b]	250-257 (4 mm Hg)	0.3 mm (200°C)	0.28 mg/ℓ[c] (24°C)	11.80	0.966 (20/20°C)	1.484 (20°C)
28553-12-3	Diisononyl phthalate	<-50	222-230 (5 mm Hg)	NA	NA	10.50	0.982 (25°C)	NA
27554-26-3	Diisooctyl phthalate	-46[b]	370	NA	NA	9.64	0.986 (20°C)	1.484 (20°)
131-11-3	Dimethyl phthalate	0	283	$4.19x10^{-3}$[d] mm Hg (20°C)	$4.32x10^{3}$ mg/ℓ (25°C)	1.56	1.189 (25/25°C)	1.5138 (25°)
84-76-3	Dinonyl phthalate	NA	413	NA	3 mg/ℓ (25°C)	10.90	0.972 (25°C)	1.4871 (20°C)
117-84-0	Di-n-octyl phthalate	-25	220-240° (4 mm Hg)	$1.44x10^{-4}$ (25°)	3.0 mg/ℓ (25°C)	5.22	0.978 (20°C)	1.482 (25°C)

TABLE 1-2 (cont.)

CAS Number	Chemical Name	Melting Point (°C)	Boiling Point (°C)	Vapor Pressure	Water Solubility	Log K_{ow}	Specific Gravity	Refractive Index
84-62-8	Diphenyl phthalate	68-70	405°C	NA	0.082 mg/ℓ (25°C)	NA	1.28 (20°C)	1.572 (74°C)
119-06-2	Ditridecyl phthalate	-37[b]	240 (2 mm Hg)	NA	0.34 mg/ℓ[c] (24°C)	15.10	0.951 (20/20°C)	1.484 (20°C)
3648-20-2	Diundecyl phthalate	2[e]	NA	NA	NA	13.14	0.954 (25°C)	1.481 (25°C)

[a] Sources: Agranoff, 1985; Dobbs and Cull, 1982; Glam et al., 1980; Grayson and Fosbraey, 1982; Hansch and Leo, 1985; Hawley, 1981; IARC, 1982; Hollifield, 1979; Leyder and Boulanger, 1983; Mabey et al., 1981; Scala and Banerjee, 1982; Schwarz, 1980; U.S. EPA, 1978c, 1980a,b; Verschueren, 1983; Wolfe et al., 1980

[b] Pour point

[c] Multicomponent mixture

[d] Calculated

[e] Freezing point

NA = Not available

acid). Many of these products are isomeric mixtures of alcohols derived from the oxo reaction of olefins--a reaction that results in the formation of alcohols with varying amounts of branching. In addition, some producers offer an ester made from a mixture of two or more alcohols. Thus, di-(heptylnonyl) phthalate may consist of diheptyl phthalate, dinonyl phthalate and heptylnonyl phthalate. The commercially available products are usually $\geq$99% pure with a residual maximum acidity of 0.01% (presumably monoalkyl phthalates containing one carboxylic acid group). The remaining impurities could be diesters of iso-phthalic acid, terephthalic acid or maleic anhydride (U.S. EPA, 1978b).

Table 1-3 lists the primary manufacturers and production sites of alkyl and aryl phthalate esters. Reported production data and estimates of production for these phthalates are presented in Table 1-4.

1.4. USE DATA

Alkyl and aryl phthalates are used as plasticizers primarily for PVC resins and less often for other vinyl resins, cellulose ester plastics, synthetic elastomers and other polymers. Plasticizer end uses are wide ranging and include construction, home furnishings, consumer goods, packaging, electrical uses, transportation and medical products (U.S. EPA, 1978b).

n-Butyl benzyl phthalate is used exclusively as a plasticizer, predominantly in vinyl flooring. The second most common use is in polyvinyl acetate emulsions used as adhesives (i.e., in the packaging industry). It has also been used as a plasticizer in acrylic resins, ethyl cellulose, polyvinyl formal and polyvinyl butyral resins (IARC, 1982).

Di-n-butyl phthalate is used mostly as a plasticizer in polyvinyl acetate emulsions for surface coatings, adhesives, and paper and textile treating (U.S. EPA, 1978b). This compound is a registered active ingredient

TABLE 1-3

Manufacturers of Alkyl and Aryl Phthalates in the United States[a]

Phthalate	Manufacturer/Location
n-Butyl benzyl	Monsanto Co., NJ
Butyl(2-ethylhexyl)	Hatco Chemical Corp., Fords, NJ
Di-n-butyl	Badische Corp., Kearny, NJ Eastman-Kodak, TN Hatco Chemical Corp., Fords, NJ Nuodex Chemical Inc., Chestertown, MD Union Camp Corp., Dover, OH U.S. Steel Corp., Neville Island, PA
Di-n-decyl[b]	Continental Oil Co., Aberdeen, NJ Eastman-Kodak, NY Tenneco Chemical Inc., Chestertown, MD
Di(2-ethylhexyl)	Badische Corp.; Kearny, NJ B.F. Goodrich Co., Avon Lake, OH Eastman-Kodak, TN Hatco Chemical Corp., Fords, NJ Monsanto Co., TX Nuodex Chemical Inc., Chestertown, MD Teknor Apex Co., Hebronville, MA U.S. Steel Corp., Neville Island, PA
Diethyl	Dynamit Nobel of America, Stony Point, NJ Eastman-Kodak, TN Morfex Chemical Co., Greensboro, NC
Diheptyl[c]	Monsanto Co., TX
Dihexyl[b]	Continental Oil Co., Aberdeen, NJ U.S. Steel Corp., Neville Island, PA
Diisodecyl	Badische Corp., Kearny, NJ Exxon Corp., Baton Rouge, LA Hatco Chemical Corp., Fords, NJ Nuodex Chemical Inc., Chestertown, MD Reichold Chemicals, Inc., Carteret, NJ Teknor Apex Co., Hebronville, MA U.S. Steel Corp., Neville Island, PA
Diisononyl	Exxon Corp., Baton Rouge, LA U.S. Steel Corp., Neville Island, PA.

TABLE 1-3 (cont.)

Phthalate	Manufacturer/Location
Diisooctyl	Reichold Chemicals, Inc., Carteret, NJ Teknor Apex Co., Hebronville, MA
Dimethyl	Dynamit Nobel of America, Inc., Stony Point, NJ Eastman-Kodak, TN Morfex Chemical Co., Greensboro, NC Sybron Corp., Lyndhurst, NJ
Dinonyl	Monsanto Co., TX Reichold Chemicals, Inc., Carteret, NJ Tenneco Chemical Inc., Chestertown, MD
Di-n-octyl[b]	Eastman-Kodak, NY Tenneco Chemical Inc., Chestertown, MD
Diphenyl[b]	Monsanto Co., MO
Ditridecyl	Exxon Corp., Baton Rouge, LA Nuodex Chemical Inc., Chestertown, MD Reichold Chemicals, Inc., Carteret, NJ Teknor Apex Co., Hebronville, MA U.S. Steel Corp., Neville Island, PA
Diundecyl[d]	Monsanto Co., TX

[a] SRI, 1985

[b] U.S. EPA, 1985b

[c] Manufactured as the mixture di(heptyl, nonyl, undecyl) phthalate

[d] Manufactured as the mixture di(heptyl, nonyl, undecyl) phthalate and as diundecyl phthalate alone

TABLE 1-4

Annual United States Production Volume of Alkyl and Aryl Phthalates

Chemical	Volume Produced (million pounds)	Year	Reference
n-Butyl benzyl phthalate	101-510	1977	U.S. EPA, 1985b
Total butyloctyl phthalates [include butyl(2-ethylhexyl) phthalate]	12.28	1982	USITC, 1983
Dibutyl phthalates (include di-n-butyl phthalate)	22.21	1984	USITC, 1985
Didecyl phthalate	1-10	1977	U.S. EPA, 1985b
Di(2-ethylhexyl) phthalate	251.1	1982	USITC, 1983
Diethyl phthalate	17.75	1984	USITC, 1985
Diheptyl phthalate	10-50	1977	U.S. EPA, 1985b
Dihexyl phthalate	0.2-2.0	1977	U.S. EPA, 1985b
Diisodecyl phthalate	145.82	1984	USITC, 1985
Diisononyl phthalate	<0.001	1977	U.S. EPA, 1985b
Diisooctyl phthalate	1-10	1977	U.S. EPA, 1985b
Dimethyl phthalate	8.64	1984	USITC, 1985
Dioctyl phthalates [include Di-n-octyl phthalate, exclude Di(2-ethylhexyl) phthalate]	301.12	1984	USITC, 1985
Diphenyl phthalate	0.1-1.0	1977	U.S. EPA, 1985b
Ditridecyl phthalate	21.79	1984	USITC, 1985
Diundecyl phthalate	10-50	1977	U.S. EPA, 1985b

in pesticides and is used as an insect repellant for textiles (U.S. EPA, 1979). Other uses are as a perfume solvent and fixative, and as a resin solvent (Hawley, 1981).

Di(2-ethylhexyl)phthalate is used in wire insulation, cloth coatings, elastomeric molded materials, extruded and calendered compositions, food packaging and in biomedical applications. The only significant non-PVC use is as a dielectric fluid in capacitors (IARC, 1982).

Diethyl phthalate is used almost entirely as a plasticizer for cellulose ester plastic films and sheets (photographic, blister packaging and tape applications) and molded and extruded articles (consumer articles such as toothbrushes, automotive components, tool handles and toys). This compound is also used as a solvent for nitrocellulose and cellulose acetate, in insecticide sprays and mosquito repellants, as a camphor substitute and as a perfume fixative and solvent (U.S. EPA, 1978a,b; Hawley, 1981).

Dihexyl phthalate is used in plastisols for carpetback coating (U.S. EPA, 1978a,b).

Di-isodecyl phthalate is used in automotive upholstery, PVC and urethane foams and in wire cable insulation with diisononyl, ditridecyl and di-noctyl phthalates (U.S. EPA, 1978a,b).

Diisononyl phthalate is used mainly as a plasticizer and has minor use as a dielectric fluid in capacitors (U.S. EPA, 1978a,b).

Dimethyl phthalate is used in solid rocket propellants, lacquers, plastics, safety glasses, rubber coating agents, molding powders and in insect repellants (Hawley, 1981) and is a registered active ingredient in pesticides (U.S. EPA, 1979).

Dinonyl phthalate is used mainly as a plasticizer and the pure grade is used as stationary liquid phase in chromatography (Hawley, 1981).

Di-n-octyl phthalate is used in plastisols for carpetback coating (U.S. EPA, 1978b) and is also a registered active ingredient in pesticides (U.S. EPA, 1979).

Diphenyl phthalate is used primarily as a plasticizer, but is also a registered active ingredient in pesticides (U.S. EPA, 1979).

Phthalates based on C_6-C_{11} alcohols are used heavily in PVC resins for automotive applications and to a lesser extent in plastisols, dispersion coatings, and in other film, sheeting, coated fabric and extrusion applications (U.S. EPA, 1978b).

1.5. SUMMARY

Alkyl and aryl phthalates are generally colorless and odorless compounds (CEH, 1975). Most alkyl phthalates are colorless liquids at ambient temperature. In general, the phthalate esters are poorly soluble in water but soluble in most organic solvents, including acetone, benzene and ether (Hawley, 1981). Phthalate plasticizers can undergo oxidation during plastic processing; antioxidants are added to resins to inhibit this reaction.

The alkyl and aryl phthalates are produced by reacting phthalic anhydride with an excess amount of the corresponding alcohol(s) in the presence of an esterification catalyst. The commercial products are usually ≥99% pure (U.S. EPA, 1978b). Sixteen U.S. manufacturers produce one or more of the 17 selected phthalic acid esters. Reported production figures and estimated production volumes were available for each of the alkyl phthalates. Total U.S. production volume of phthalic acid esters amounted to 1179 million pounds in 1984 (USITC, 1985). Alkyl and aryl phthalates are used predominantly as plasticizers for polyvinyl chloride resins (U.S. EPA, 1978a,b). To a lesser extent, they are used as plasticizers for other vinyl resins, cellulose ester plastics, synthetic elastomers and other polymers.

End-uses include construction, home furnishing, consumer goods, packaging, electrical uses, transportation and medical products (U.S. EPA, 1978a,b). Some alkyl esters have minor applications as dielectric fluid [di(2-ethylhexyl)phthalate], active ingredients in pesticides, resin solvents, perfume fixatives, solvents and other uses (Hawley, 1981; U.S. EPA, 1979).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

2.1.1. Hydrolysis. Limited data regarding the hydrolysis of the phthalic acid esters were located in the available literature as cited in the Appendix. Gledhill et al. (1980) observed <5% hydrolysis of 1 mg/ℓ n-butyl benzyl phthalate in 28 days. Wolfe et al. (1980) estimated second-order rate constants for alkaline hydrolysis of phthalates at pH 10-12 and 30°C.

Rate constants varied with the size and complexity of the phthalates and ranged from $1.1\text{x}10^{-4}$ M^{-1} sec^{-1} for di(2-ethyhexyl) phthalate to $6.9\text{x}10^{-2}$ M^{-1} sec^{-1} for dimethyl phthalate. Thus, corresponding estimated half-lives at pH 7 range from 3.2-2000 years, respectively. The hydrolysis half-lives of diphenyl and di-t-butyl phthalates at a pH of 7 are estimated to be 35 days and 12,000 years, respectively (Suffet et al., 1981). Hydrolysis may not result in significant degradation of most phthalate esters compared with other mechanisms such as microbial degradation.

2.1.2. Oxidation. No experimental data pertaining to the oxidation of alkyl and aryl phthalates in water were located in the available literature as cited in the Appendix. Mabey et al. (1981) calculated RO_2 radical reaction rate constants for phthalate esters, which become larger with increasing size and complexity of the phthalate ester chains. Values range from 0.05 M^{-1} sec^{-1} for dimethyl phthalate to 7.2 M^{-1} sec^{-1} for di(2-ethylhexyl) phthalate and 280 M^{-1} sec^{-1} for n-butyl benzyl phthalate. Assuming an ambient RO_2 radical concentration of 10^{-9} M, (Mill et al., 1980), oxidation half-lives were calculated to be >3 years for the alkyl phthalates. A significantly shorter half-life of ~29 days was calculated for n-butyl benzyl phthalate using data from Mabey et al. (1981).

Mabey et al. (1981) predicted that reaction of phthalates with singlet oxygen would not be environmentally important.

The interaction of alkyl phthalates with OH radicals present in normal ambient water is considered to be too slow to be of importance (Callahan et al., 1979a).

2.1.3. **Photolysis.** Gledhill et al. (1980) studied the photolysis of aqueous n-butyl benzyl phthalate in sealed tubes. The photolysis half-life was >100 days. Experimental data regarding the photolysis of alkyl phthalates in water were not located in the available literature as cited in the Appendix; however, the UV absorption spectra for di-n-butyl, di(2-ethylhexyl), diethyl, dimethyl and di-n-octyl phthalates in organic solvents indicates slight absorption at wavelengths of 290nm. The absorption becomes even less significant at longer wavelengths and no absorption occurs above 310 nm (Sadtler, n.d.). This information indicates that although the potential for direct photolysis exists, the photolysis of phthalates in ambient waters may not be significant.

2.1.4. **Microbial Degradation.** Phthalate esters have been reported to be metabolized in water by pure cultures of microorganisms, mixed microorganisms and in natural water. The rates of degradation vary widely depending upon environmental conditions, such as temperature, pH, amount of dissolved oxygen and the structure of phthalate (Hattori et al., 1975). The degradation of phthalate esters by pure culture isolated from natural water, activated sludge and soil have been studied by several investigators (Taylor et al., 1981; Kurane et al., 1979a,b; Engelhardt et al., 1975, 1977; Engelhardt and Wallnofer, 1978; Klausmeier and Jones, 1960; Perez et al., 1977; Ohta and Nakamoto, 1979). Several authors have studied the biodegradation of phthalate esters by mixed microorganisms. Thus, activated sludge, domestic wastewater and natural river water have been used as microbial inoculum to study the biodegradation of phthalate esters (O'Grady et al., 1985; Saeger and Tucker, 1973b, 1976; Sasaki, 1978; Sugatt et al., 1984). Tabak et al. (1981) observed 100% degradation of dimethyl, diethyl, di-n-butyl and butyl benzylphthalate in 7 days with unacclimated microorganisms from domestic wastewater. On the other hand, bis-(2-ethylhexyl) phthalate and di-n-octyl phthalate needed 21 days of acclimatization before a biodegradation of >90% in 7 days were observed (Tabak et al., 1981). Similarly, the mineralization of >85% occurred with various phthalates in 28 days with both activated sludge and river water (Saeger and Tucker, 1976; Sugatt et al., 1984). The metabolic pathway data indicate that phthalate esters first undergo enzymatic hydrolysis to form the monoester, followed by further hydrolysis to phthalic acid. The phthalic acid is further degraded to carbon dioxide and water (U.S. EPA, 1978b; Saeger and Tucker, 1976).

Results of various river die-away studies using a few phthalate esters are presented in Table 2-1. Saeger and Tucker (1973a,b, 1976) and Gledhill et al. (1980) concluded from their river die-away and activated sludge studies that phthalate plasticizers, as a class, undergo rapid primary degradation and mineralization by bacteria commonly found in the environment. In a simulated lake microcosm, Gledhill et al. (1980) observed >95% primary degradation of n-butyl benzyl phthalate in 7 days (C_0=1 mg/ℓ). The biodegradation half-life for n-butyl benzyl phthalate in this natural water system was <4 days. The length and configuration of the alkyl ester chains significantly influences the biodegradation rate of phthalates in freshwater ecosystems, whereas acclimation of microbes appears to have little effect (Hattori et al., 1975; Johnson et al., 1984). In freshwater systems, phthalates such as dimethyl and diethyl phthalate are expected to

TABLE 2-1

Biodegradation Screening of Some Alkyl and Aryl Phthalates[a]

Phthalate	River Die-Away, Unacclimated System			River Die-Away, Unacclimated System[d]		
	% Primary Degradation[b]	t[b] (weeks)	$t_{1/2}$[c] (weeks)	% Primary Degradation	t (days)	$t_{1/2}$ (days)
n-Butyl benzyl	100	1.3	0.2	100	9	2
Di(2-ethylhexyl)	40	5.0	2.5	NA	NA	NA
Di(hexyl, nonyl, undecyl)	55	5.0	NA	NA	NA	NA
Di(hexyl, octyl, nonyl, decyl, undecyl)	NA	NA	3.0	NA	NA	NA
Diundecyl	20	5.0	2.5	NA	NA	NA

[a] Initial concentrations = 1 mg/ℓ

[b] Saeger and Tucker, 1973a

[c] Saeger and Tucker, 1973b

[d] Gledhill et al., 1980

NA = Not available

degrade faster than the larger and more complex phthalate esters (Johnson et al., 1984; Hattori et al., 1975). Hattori et al. (1975) observed 100% decomposition of diethyl phthalate after 6 days and 100% decomposition of dimethyl phthalate after 8-11 days in river water initially spiked with 25 mg/ℓ of the ester. Di(2-ethylhexyl) phthalate degraded only ~40% after 2 weeks in river water. In relatively clean ocean water, ~14-20% degradation of diethyl and dimethyl phthalate was measured after 14 days, while the larger phthalates were decomposed >30% during the same period. The degradation of all the phthalate esters were much higher with polluted ocean water. For example, while 33% of dibutyl phthalate and 14% of diethyl phthalate degraded in clean ocean water in 14 days, the degradation was 100% in 5 days for dibutyl phthalate and 68% in 14 days for diethyl phthalate with polluted ocean water. The higher degradation in polluted water was attributed to the presence of higher concentrations and nutrients in polluted water. Longer chain phthalate esters decomposed faster than dimethyl and diethylphthalates in clean ocean water, a finding not further explained (Hattori et al., 1975).

In aquatic sediments under anaerobic conditions, biodegradation of short chain alkyl esters appears to be slow and degradation of the longer chain esters has been observed to be very slight or undetectable (Johnson et al., 1984; Johnson and Lulves, 1975; Horowitz et al., 1982; Shelton et al., 1984). Johnson and Lulves (1975) observed 61 and 98% anaerobic mineralization of di-n-butyl phthalate in 14 and 30 days, respectively. Under the same conditions, no detectable degradation of di(2-ethylhexyl) phthalate was measured after 30 days. Johnson et al. (1984) measured 10% anaerobic mineralization of radiolabeled di(2-ethylhexyl) phthalate after 28 days and <1% mineralization of diisononyl and diisooctyl phthalates. Optimal degradation of long chain phthalates occurred at high concentrations in nutrient-rich aquatic sediments with temperatures above 22°C. Such environmental conditions are typical of sewage treatment ponds, wetlands, eutrophic lakes and enriched streams during summer. Winter conditions, particularly at northern latitudes and environmentally realistic (low, <1 μg/ℓ) concentrations would adversely affect biodegradation (Johnson et al., 1984).

2.1.5. **Volatilization.** No significant volatility losses (<0.5%/24 hours) were observed for n-butyl benzyl, di(2-ethylhexyl), di(hexyl, nonyl, undecyl) and diundecyl phthalates during biodegradation studies with activated sludge (Saeger and Tucker, 1976). Atlas et al. (1982) measured the mass-transfer coefficient of di-n-butyl phthalate to be 0.104 cm/hour in stirred (200-300 rpm) seawater free of interfering organic contaminants at 23°C. At a depth of 4.5 cm, the volatilization half-life of di-n-butyl phthalate has been calculated to be 30 hours following the method of Dilling (1977).

Henry's Law constants for some phthalate acid esters, calculated using vapor pressure and water solubility data from Table 1-2 are as follows:

di-methyl phthalate	2.5×10^{-7} atm•m^3/mol
di-ethyl phthalate	7.8×10^{-7} atm•m^3/mol
di-n-butyl phthalate	2.2×10^{-6} atm•m^3/mol
di-n-octyl phthalate	2.4×10^{-5} atm•m^3/mol
di-(2-ethylhexyl)phthalate	1.1×10^{-7} atm•m^3/mol
n-butyl benzyl phthalate	1.2×10^{-6} atm•m^3/mol

This information also suggests that volatilization would not be a significant removal process for these phthalate esters, except di-n-octyl phthalate, which could volatilize significantly from shallow rivers (Lyman et al., 1982). The evaporation half-life of di(2-ethylhexyl) phthalate from bodies of water has been estimated to be 15 years (Callahan et al., 1979a).

2.1.6. **Adsorption.** Sullivan et al. (1982) studied the adsorption of di-n-butyl and di(2-ethylhexyl) phthalates onto clay minerals, calcite and sediment samples from seawater. Results indicate that adsorption increases with increased salinity or decreased solubility of phthalates. Adsorption onto the clay minerals and calcite appeared to be a reversible process, whereas adsorption onto sediments was irreversible. This suggests that marine sediments may act as a final repository of phthalic acid esters (Sullivan et al., 1982). Mabey et al. (1981) calculated sediment-water partition coefficients for phthalates, indicating adsorption is likely for all phthalate esters with adsorption tendency increasing with size and branching of the ester chain. Sediment adsorption coefficients range from 98 for dimethyl phthalate to >150,000 for di-n-butyl phthalate and the larger phthalate esters including n-butyl benzyl phthalate. Gledhill et al. (1980) observed significant partitioning of n-butyl benzyl phthalate to sediments in a simulated lake microcosm. The average ratio of this compound measured in sediments versus water was 571:1.

The contention that phthalates will be adsorbed significantly onto sediments in aquatic ecosystems is supported by the observation that phthalates are commonly found in bottom sediments from both streams and seas (Callahan et al., 1979a).

Evidence suggests that complexation of phthalates in natural water with organic substances may be one mode of transport of phthalates (Khan, 1980; Ogner and Schnitzer, 1970; Matsuda and Schnitzer, 1971). Phthalate esters have been observed readily interacting with fulvic acid, a widely occurring humic substance found in soils and waters. The phthalates appear to adsorb to the surface of the fulvic acid molecule rather than react with it. The fulvic acid-phthalate complex is very soluble in water; thus, mobility of otherwise insoluble phthalate esters is modified. Extent of solubilization appears to vary with phthalate size. Equivalent quantities of fulvic acid will solubilize 4 times as many equivalents of di(2-ethylhexyl) phthalate as of di-n-butyl phthalate (Matsuda and Schnitzer, 1971).

2.1.7. **Bioaccumulation.** Phthalate esters have been identified in living matter, and data collected from field and laboratory studies indicate that these compounds can be taken up and bioaccumulated in a variety of organisms. The majority of data is on di(2-ethylhexyl) phthalate (Callahan et al., 1979a). Most phthalates have relatively high K_{ow} values (>250), suggesting lipophilicity and potential for bioconcentration. Studies pertaining to the uptake and bioaccumulation of phthalate esters in aquatic organisms are discussed in Chapter 6.

2.2. AIR

2.2.1. **Chemical Degradation.** Limited data regarding the degradation of the phthalate esters in the atmosphere are available in the literature as cited in the Appendix. The HO radical reaction half-life of gaseous dimethyl, di-n-butyl, di(2-ethylhexyl) and n-butyl benzyl phthalates at 25°C have been estimated to be 23.80, 18.44, 11.86 and 14.29 hours, respectively, by the GEMS programming method (U.S. EPA, 1986a).

The same GEMS programming method predicts that reaction of phthalates with atmospheric ozone is not a significant process (U.S. EPA, 1986a).

The UV absorption spectra for di-n-butyl, di(2-ethylhexyl), diethyl, diisodecyl and di-n-octyl phthalate reveal slight absorption of UV light at wavelengths >290 nm although no absorption occurs at wavelengths >310 nm (Sadtler, n.d.). These data suggest that although there is a potential for photodegradation in the atmosphere, the process is probably not a significant one.

2.2.2. **Physical Removal.** Monitoring data reveal that phthalate esters can be removed from the atmosphere by wet and dry deposition (Kawamura and Kaplan, 1983; Atlas and Giam, 1981; Karasek et al., 1978; Weschler, 1984).

Average measured ratios of the concentration in precipitation to air are 3.56×10^4 and 3.93×10^4 for di-n-butyl phthalate and di(2-ethylhexyl) phthalate, respectively (Atlas and Giam, 1981). This indicates significant removal of atmospheric phthalates through precipitation. The probability of removal of an atmospheric pollutant through adsorption on atmospheric aerosols and subsequent precipitation is reasonable for chemicals with saturation vapor pressures of $\leq10^{-7}$ mm Hg (Cupitt, 1980). Since the vapor pressures of all the phthalates, listed in Table 1-2, with the exception of di(2-ethyl hexyl) phthalate, are $<10^{-7}$ mm Hg, they are not likely to be removed significantly by this mechanism. Di(2-ethylhexyl) phthalate, on the other hand, may be significantly removed.

2.3. SOIL

2.3.1. Chemical Degradation. Pertinent data regarding the chemical degradation of phthalate esters in soil could not be located in the available literature as cited in the Appendix. Considering data presented in Section 2.1., hydrolysis in wet soils (excluding diphenyl phthalate) and photolysis at soil surfaces would not be important degradation mechanisms.

2.3.2. Microbial Degradation. Shanker et al. (1985) observed microbial degradation of di-n-butyl, di(2-ethylhexyl) and dimethyl phthalates in garden soil. Results of this study are listed in Table 2-2. This investigation indicates soil microflora significantly degraded phthalates under aerobic conditions, and shorter chain phthalates degraded at a faster rate than the compounds with longer chains. The anaerobic degradation of phthalates was much slower than the aerobic degradation. In various other studies, a considerable number of widely occurring microorganisms capable of degrading phthalate esters, such as Nocardia, Arthrobacter, Pseudomonas and the fungus Penicillium lilacinium, have been isolated from soils and other

TABLE 2-2

Biodegradation of Phthalates in Garden Soil[a,b]

Incubation Time (days)	Dimethyl Phthalate				Di-n-butyl Phthalate				Di(2-ethylhexyl)phthalate			
	Aerobic		Anaerobic		Aerobic		Anaerobic		Aerobic		Anaerobic	
	DMP	PA	DMP	PA	DNBP	PA	DNBP	PA	DEHP	PA	DEHP	PA
0	468±16	0	471±12	0	472±14	0	470±17	0	480±9	0	478±9	0
5	180±11	9±0.5	410±8	8±1.1	110±13	8±0.6	402±9	12±1.1	430±8	8±1.1	460±8	traces
10	43±9	8±0.5	376±6	10±0.5	40±6	6±0.6	348±8	14±2.9	320±11	7±1.1	439±6	2±0
15	0	0	302±10	24±1.7	0	0	301±9	29±3.5	NA	NA	NA	NA
20	0	0	245±6	9±1.1	0	0	239±9	22±2.3	120±4	11±0.6	389±5	8±1.1
30	0	0	178±2	3±1.0	0	0	159±4	15±1.7	40±8	5±0.6	318±7	11±0.6
Autoclaved control	465±6	traces	467±8	0	465±10	traces	463±9	0	471±4	0	478±7	0

[a]Source: Shanker et al., 1985

[b]Each value is the mean±SE of triplicate samples in μg compound recovered/g soil

PA = Phthalic acid

NA = Not available

natural sources (Kurane et al., 1977; Ohta and Nakamoto, 1979; Englehardt and Wallnofer, 1978; Englehardt et al., 1977; Williams and Dale, 1983; Lewis et al., 1984; Klausmeier and Jones, 1960). In view of this information as well as the aquatic biodegradation data (see Section 2.1.4.), significant removal of phthalate esters may be possible under aerobic conditions; however, anaerobic degradation may be a very slow removal mechanism.

2.3.3. Volatilization. Pertinent data regarding the volatilization of alkyl and aryl phthalic acid esters from soil surfaces could not be located in the available literature as cited in the Appendix. Considering the tendency of the larger phthalates to adsorb to soils (Section 3.2.4.) as well as their relatively low vapor pressures, volatilization will probably not be an important removal mechanism. Since dimethyl phthalate is not likely to adsorb to soils, volatilization from dry soil surfaces may be a potential removal mechanism for this compound.

2.3.4. Adsorption. Pertinent data regarding the adsorption of alkyl and aryl phthalates to soils could not be located in the available literature as cited in the Appendix. Wide ranging water solubilities and K_{ow} values suggest that adsorption to soils by the phthalate esters is dependent upon the size and complexity of the phthalate ester chains. Mobility of phthalates in soil has been categorized using adsorption coefficients obtained from the following equation (Kenaga, 1980): $\log K_{oc} = 3.64-0.55 \log WS$. From this equation, dimethyl phthalate should predictably be highly mobile in soils (K_{oc}=44). n-Butyl benzyl, di-n-butyl, di-n-octyl and dinonyl phthalates should be low to slightly mobile (K_{oc} 890-2400), while larger or branch-chained compounds, including diphenyl phthalate, should remain strongly adsorbed to soils (K_{oc}>5000). Data presented in Section 2.1. indicate that the mobility of phthalates is affected, and expectably enhanced, by the presence of fulvic acid in soils.

2.4. SUMMARY

Hydrolysis is not expected to be a significant removal mechanism of phthalate esters (Suffet et al., 1981). Mabey et al. (1981) estimated that phthalate esters will not undergo significant oxidation in water. UV absorption spectra for some phthalates in nonaqueous solvents indicate that potential exists for direct photolysis in the environment. The photolysis half-life of n-butyl benzyl phthalate has been observed to be >100 days (Gledhill et al., 1980). Phthalate esters are reported to be metabolized in the aquatic environment by a variety of pure microorganisms and degraded by mixed microbial systems. The microbial degradation rates vary widely depending upon environmental conditions such as temperature, pH, amount of oxygen present and the phthalate structure (Thomas et al., 1984; Hattori et al., 1975). Biodegradability of phthalates in freshwater decreases with increasing size and complexity of the phthalate ester chains (Hattori et al., 1980; Johnson et al., 1984).

Results from river die-away tests and activated sludge studies indicate that phthalates, as a class, undergo rapid degradation by bacteria commonly found in the environment (Saeger and Tucker, 1973a,b, 1976; Gledhill et al., 1980). For example, in a simulated lake microcosm Gledhill et al. (1980) observed >95% primary degradation of the complex ester n-butyl benzyl phthalate in 7 days. Under anaerobic conditions, biodegradation of short-chain alkyl esters has been shown to be possible, but slower than under aerobic conditions, while degradation of the long-chain esters has been shown to be very slight or undetectable (Johnson et al., 1984; Johnson and Lulves, 1975; Horowitz et al., 1982; Shelton et al., 1984). From the estimated Henry's Law Constants for n-butyl benzyl, di-n-butyl, di(2-ethylhexyl), diethyl, dimethyl and di-n-octyl phthalates, phthalate esters are predicted to not significantly volatilize from water (Lyman et al., 1982). Di-n-octyl phthalate may significantly volatilize from shallow rivers, although volatilization from deeper waters should not be significant (Lyman et al., 1982). In seawater, adsorption onto clay minerals and calcite appears to be a reversible process, whereas adsorption onto sediments is irreversible (Sullivan et al., 1982). This suggests that marine sediments may act as a final repository of phthalic acid esters (Sullivan et al., 1982). Calculated sediment-water partitioning coefficients indicate adsorption is likely for all phthalate esters, with adsorption tendency increasing with the size and complexity of the ester chain (Mabey et al., 1981). Complexation with the widely occurring humic and fulvic substances causes solubilization of phthalate esters in water, thus modifying their mobility (Matsuda and Schnitzer, 1971). Phthalates have been identified in living matter, and data collected from field and laboratory studies indicate that these compounds can bioaccumulate in aquatic organisms (Callahan et al., 1979a).

In air, the phthalate esters, as a class, are predicted to react with hydroxyl radicals, with a $t_{1/2}$ of <1 day (U.S. EPA, 1986a). The actual atmospheric $t_{1/2}$, however, may be longer than the estimated values because of adsorption onto airborne particulate matter. Removal of atmospheric phthalate by wet and dry deposition has also been observed (Kawamura and Kaplan, 1983; Atlas and Giam, 1981; Karasek et al., 1978; Weschler, 1984).

Significant hydrolysis of phthalate esters in wet soils is unlikely (Wolfe et al., 1980; Gledhill et al., 1980). Shanker et al. (1985) observed microbial degradation of di-n-butyl, di(2-ethylhexyl) and dimethyl phthalates in garden soil. Results indicate that soil microflora significantly degrade phthalates under aerobic conditions, and short-chain phthalates degrade at a faster rate than the longer chain phthalates. The anaerobic degradation of phthalates was very slow compared with aerobic biodegradation. The water solubilities and K_{ow} values of the phthalates suggest that adsorption to soils is dependent on the size and complexity of phthalate ester chains. Dimethyl phthalate should be reasonably mobile in soils, whereas large or branched chain esters, including diphenyl phthalate, should remain strongly adsorbed to soils. The mobility of phthalate esters in the presence of fulvic acid should increase. Since dimethyl phthalate is not likely to adsorb to soils, volatilization from dry soil surfaces may be a potential removal mechanism. Volatilization will be insignificant for other phthalates.

3. EXPOSURE

Phthalate esters are ubiquitious in the environment. They have been found in underground and drinking waters, surface waters, soil, oil, food, plants, fish, animals and humans (Callahan et al., 1979a). There is some evidence that phthalate esters occur naturally in certain plants and organisms (Callahan et al., 1979a; Peakall, 1975; Mathur, 1974). The environmental contribution of phthalate esters from anthropogenic sources, however, far exceeds its contribution from natural sources. The disposal of plastic materials containing phthalate esters in disposal sites constitutes the major reservoir of these compounds in the environment (Mathur, 1974; Peakall, 1975). All these environmental media containing phthalate esters may directly or indirectly cause human exposure to these compounds. The leaching of phthalate esters from the hemodialysis tubing and the PVC bags containing intravenous solutions can be sources of exposure to these compounds for a special segment of the population. A considerable body of research has been done in this area (Ono et al., 1975; Corley et al., 1977; Pollack et al., 1985b; Fayz et al., 1977). The levels of these compounds in water, air and food and possible human exposure to phthalate esters from these sources are discussed in the following sections.

3.1. WATER

Phthalate esters have been detected in industrial effluents by several investigators. Jungclaus et al. (1976) reported the presence of diethyl phthalate at a concentration of 60 μg/ℓ (60 ppb) in the wastewater from a tire manufacturing plant. In a survey of effluents from the petroleum refining industry, Snider and Manning (1982) reported the detection of dimethyl, diethyl, di-n-butyl, di(2-ethylhexyl) and n-butyl benzyl phthalates in both the biotreatment effluents and final effluents of the treated wastewaters. The concentrations of dimethyl, diethyl and n-butyl benzyl phthalates in the final effluents were always <20 µg/ℓ (ppb), but final effluents from one type of refinery wastewater had a di-n-butyl phthalate concentration in the range of 2-32 µg/ℓ. In another class of refinery, the concentration range of di(2-ethylhexyl) phthalate in the final effluents was reported to be <0.1-2000 µg/ℓ (Snider and Manning, 1982). Hites and Lopez-Avila (1980) reported the presence (concentration not quantified) of dioctyl and di(2-ethylhexyl) phthalates in wastewaters from an unspecified specialty chemical manufacturing plant. The average concentrations of diethyl, di(2-ethylhexyl), di-n-octyl, di-n-butyl and n-butyl benzyl phthalates in 76 sources of pollution into the influent of sewage treatment plants of two cities were reported to range from 16.2-22.0, 19-46, 33-62.5 and 16-17 µg/ℓ, respectively (Callahan et al., 1979b). Other authors have detected dimethyl, diethyl, dibutyl, diisobutyl and dioctyl phthalates in the treated effluents from pulp and paper manufacturers (Voss, 1984; Brownlee and Strachan, 1977; Fox, 1977). The concentrations of diethyl, dibutyl and dioctyl phthalates in the effluents were reported to be 50, 70 and 15 µg/ℓ, respectively (Brownlee and Strachan, 1977; Voss, 1984).

Phthalate esters were also identified in the influents and effluents of sewage treatment plants (Thomson et al., 1981; McCarty and Reinhard, 1980; Ellis et al., 1982; Hites, 1979; Callahan et al., 1979b). The concentrations of dimethyl, diethyl, di-n-butyl, diisobutyl, di(2-ethylhexyl) and n-butyl benzyl phthalates in sewage influent were reported to be as high as 6.0, 17, 50, 3.0, 200 and 40 µg/ℓ, respectively (Callahan et al., 1979b; McCarty and Reinhard, 1980; Hites, 1979). The removal of the phthalate esters as a result of treatment of wastewater evidently depends on the nature of treatment. For example, Callahan et al. (1979a) reported almost complete removal of diethyl, di(2-ethylhexyl), n-octyl and n-butyl benzyl phthalates in the effluent from a sewage treatment plant. Other investigators have observed partial removal or, in some cases, increases in the concentrations of phthalate esters in the effluent from sewage treatment plants (Young et al., 1983; Hites, 1979; McCarty and Reinhardt, 1980). Thus, although the concentration of di(2-ethylhexyl) phthalate in the influent water of the Los Angeles County sewage treatment plant was 42 μg/ℓ, the treated effluent had a reported concentration of 420 μg/ℓ (Young et al., 1983). Other investigators have identified the presence of diethyl, di-n-butyl and di(2-ethylhexyl) phthalates in the wastewater from a poultry plant, which had undergone wastewater treatment and reclamation, and in wastewater from a dining hall, laboratory and dormitory of a Japanese university (Shibuya, 1979; Andelman et al., 1984).

Phthalate esters have been identified in surface waters throughout the United States. The presence of dimethyl phthalate in surface waters around the contaminated area in Love Canal, Niagara Falls, NY, was reported by Hauser and Bromberg (1982). The concentrations of dibutyl, di(2-ethylhexyl) and n-butyl benzyl phthalates in Delaware River water 2 miles downstream from a Philadelphia wastewater treatment plant were reported to be 0.6, 1.0 and 0.6 μg/ℓ, respectively (Hites, 1979). Dewalle and Chian (1978) also identified dibutyl, diethyl and hexyl esters and an unidentified phthalate in Delaware River water and its major tributaries; diethylhexyl phthalate occurred in these waters with a 90% frequency. The concentrations of phthalate esters in Delaware River water between Marcus Hook, PA, and Trenton, NJ, was reported to be higher in winter than in summer (Sheldon and Hites, 1978). The reported concentration ranges for dibutyl, dioctyl and butyl benzyl phthalates in this riverwater during the winter of 1976-1977 were 0.2-0.6, 3.0-5.0 and 0.4-1.0 µg/ℓ, respectively. Goodley and Gordon (1976) reported the presence of diethyl, di-n-butyl and di-n-octyl phthalates in lower Tennessee River water near Calvert City, KY. Corcoran (1973) reported the concentration of di(2-ethylhexyl) phthalate in Mississippi River water to be (tentatively) as high as 600 µg/ℓ. The concentration further downstream in the water of Escambia Bay, FL, was much less (not quantified), and the concentration was even less (not quantified) in the water of the Gulf Stream. Murray et al. (1981) identified di(2-ethylhexyl) phthalate in the water from Galveston Bay, TX, at a mean concentration of 0.6 µg/ℓ. Other investigators have identified dibutyl, diethyl and dioctyl phthalates in water from lower Fox River, WI (Peterman et al., 1980). Results of an extensive survey designed to determine the levels of butyl benzyl phthalate in surface waters near various industrial sites in the United States are reported in Table 3-1.

Phthalate esters also have been identified in river waters in other countries, including the Rhine, Ijssel, Mense and Waal rivers in the Netherlands (Schouten et al., 1979; Meijers and VanderLeer, 1976), in the Kiel Bright in Germany (Ehrhardt and Derenbach, 1980), in the Caroni River, Trinidad (Moore and Karasek, 1984), and in the River Glatt, Switzerland (Zuercher and Giger, 1976). The maximum reported concentrations of di-n-butyl phthalate and di(2-ethylhexyl) phthalate in these foreign waters were 2.8 µg/ℓ (Ijssel River) and 4.1 µg/ℓ (Mense River), respectively (Schouten et al., 1979).

Rainwater collected from West Los Angeles, CA, during 1981-1982 contained a maximum of 9.0 µg/ℓ of total phthalate esters (Kawamura and

TABLE 3-1

Concentrations of n-Butyl Benzyl Phthalate in United States Waters Near Industrial Sites*

Sampling Site	Concentration in Water (μg/ℓ) 1980	1981	1982
Alabama River, Mobile, AL	ND	NS	ND
Baltimore Harbor, Sparrow's Point, MD	NS	NS	ND
Charles River, Boston, MA	NS	ND	NS
Chesapeake Bay, Fisherman IS, MA	ND	ND	ND
Delaware Bay, Lewes, DE	ND	ND	ND
Delaware River, Port Penn, DE	ND	ND	ND
Delaware River, Wilmington, DE	ND	NS	ND
Detroit River, Gilwater, MI	NS	NS	ND-0.35
Illinois River, Joliet, IL	NS	0.6-0.9	NS
Kanawha River, Nitro, WV	NS	NS	ND-0.3
Kanawha River, Winfield Dam, WV	NS	NS	ND
Lake Erie, Erie, PA	ND	ND	NS
Lake Huron, Saginaw Bay, MI	ND	ND	ND
Lake Michigan, Charlevoix, MI	ND	ND	ND
Lake Michigan, Calumet, IL	ND	ND	ND
Lake Oneida, Verona Beach, NY	NS	ND	NS
Lake Ontario, Four Mile Creek, NY	NS	NS	ND
Lake Superior, Sault St. Marie, MI	ND	ND	ND-0.45
Mississippi River, St. Paul, MN	ND	ND	NS
Mississippi River, above St. Lonis, MO	ND	ND	ND
Mississippi River, below St. Louis, MO	NS	NS	ND-0.85
Mississippi River, Memphis, TN	ND	ND	ND
Missouri River, St. Louis, MO	ND	ND	ND
Mobile Bay, Ft. Morgan, AL	ND	NS	NS
Niagara River, Sandy Beach, NY	NS	NS	ND
Ohio River, Gallipolis Ferry, OH	NS	NS	ND
Ohio River, Pittsburg, PA	NS	NS	ND-0.3
Potamac River, Popes Creek, MD	ND	ND	NS
Saginaw River, Bay City, MI	NS	NS	ND
San Francisco Bay, Brooks Island, CA	ND	NS	ND-0.3

*Source: Michael et al., 1984

NS = Not sampled

ND = Not detected with the detection limits being 0.5, 0.5 and 0.3 μg/ℓ in 1980, 1981 and 1982, respectively.

Kaplan, 1983). Dimethyl, diethyl, di-n-butyl, di-n-octyl, di(2-ethylhexyl) and n-butyl benzyl phthalate esters have been identified in urban runoff waters at concentration ranges of 2-10, 0.5-11.0, 0.4-1, 7-39 and 10.0 µg/ℓ, respectively (Cole et al., 1984). From their survey of contamination of Japanese rivers, Takana et al. (1978) concluded that only 10% of the phthalate ester load in river waters is attributable to atmospheric precipitation and 90% to wash off following periods of rain.

Phthalate esters have also been identified in groundwater from contaminated sites. In a system developed to study the trace organic removal efficiency by an infiltration site in Phoenix, AZ, Tomson et al. (1981) reported complete removal of dimethyl phthalate from sewage water (0.023 µg/ℓ initial conc.) passed through a 60-foot deep infiltration basin. The removal of diethylphthalate was ~93%, but dibutyl phthalate concentration was observed to increase as a result of infiltration. Francis et al. (1980) specified dibutyl, diethyl and several unidentified phthalates in leachates from radioactive waste disposal sites at Maxey Flats, KY, and at West Valley, NY. Dunlap et al. (1976a,b) detected several phthalate esters in groundwater from a landfill site near Norman, OK; concentrations of diethyl, diisobutyl and dioctyl phthalates were 4.1, 0.1 and 2.4 µg/ℓ, respectively (Dunlap et al., 1976a,b). Groundwater samples from a well at General Electric's capacitor manufacturing facility in Ft. Edward, NY, contained di(2-ethylhexyl) phthalate (Welch, 1982). Hutchins et al. (1983) identified dimethyl, diethyl, dibutyl and di(2-ethylhexyl) phthalates in groundwaters at infiltration sites of secondary effluents at Ft. Devens, MA; Boulder, CO; Lubbock, TX; and Phoenix, AZ. The maximum reported concentrations of dimethyl, diethyl, dibutyl and di(2-ethylhexyl) phthalates in these groundwaters were 0.19, 0.87, 2.38 and 1.40 µg/ℓ, respectively. DeWalle and Chian (1981) reported dibutyl and di(2-ethylhexyl) phthalates at concentrations up to 1 and 100 µg/ℓ in groundwaters from a landfill site in New Castle County, DE. Leachate from a landfill site in Broome County, NY, contained various phthalate esters, including diethyl phthalate at 15 µg/ℓ (Russell and McDuffie, 1983). Diethyl phthalate at 0.3 µg/ℓ concentration was identified in groundwater from a contaminated site in the Netherlands (Zoeteman et al., 1981).

The concentrations of several phthalate esters in effluents and ambient waters are given in Table 3-2.

Several phthalate esters have been identified in drinking water abstracted from groundwater and surface water in the United States and elsewhere. The concentrations of four most frequently occurring phthalate esters detected in the U.S. drinking waters are given in Table 3-3. It is evident from Table 3-3 that even the most frequently occurring phthalate esters do not occur in all U.S. drinking waters. In a National Organics Reconnaissance Survey of drinking waters from 10 U.S. cities (Seattle, WA; New York, NY; Miami, FL; Tuscon, AZ; Ottumwa, IA; Grand Forke, ND; Cincinnati, OH; Lawrence, MA; Philadelphia, PA; and Terrebonne Parish, LA), both di-n-butyl and diethyl phthalate occurred in 60% of those waters (Bedding et al., 1982). The Science Advisory Board of U.S. EPA reviewed selected organic chemicals and estimated that the distribution of the phthalate esters is ~50% in U.S. drinking waters, with an overall phthalate concentration of ~0.1 µg/ℓ (U.S. EPA, 1975).

Levins et al. (1979) reported in a survey of water from Cincinnati, St. Louis, Atlanta and Hartford that the following percentages of samples from each category contained the designated phthalates (Table 3-4).

TABLE 3-2

Median Concentration of Phthalate Esters in Industrial Effluents and Ambient Water in the United States Compiled from STORET Stations[a,b]

Phthalate	Median Concentration (μg/ℓ)	Number of Samples	Frequency of Occurrence (%)
	EFFLUENTS		
Dimethyl phthalate	<10.0	1255	2.8
Diethyl phthalate	<10.0	1286	9.9
Di(2-ethylhexyl) phthalate	10.0	1385	38.9
n-Butyl benzyl phthalate	<6.0	1337	7.2
	AMBIENT WATERS		
Dimethyl phthalate	<10.0	836	0.6
Diethyl phthalate	<10.0	862	3.0
Di(2-ethylhexyl) phthalate	10.0	901	24.0
n-Butyl benzyl phthalate	<10.0	1220	3.0

[a] Source: Staples et al., 1985

[b] The authors used U.S. EPA STORET data only from the 1980s because better quality control practices were used to develop the data at that time.

TABLE 3-3

Concentrations of Commonly Reported Phthalate Esters Detected in Drinking Waters in the United States

Location	Source of Raw Water	Concentrations of Phthalate Esters[a] (μg/ℓ)				Reference
		DEP	DBP	DEHP	BBP	
Thirty-nine public water wells in New York State	groundwater	4.6[b] (33)	470.0[b] (54)	170.0[b] (92)	38.0[b] (13)	CEQ, 1980, 1981; Burmaster, 1982
Waters from Torresdale Treatment Plant in Philadelphia, PA	surface	NQ	0.1 (NA)	0.6 (NA)	0.1 (NA)	Hites, 1979; Suffet et al., 1980
District of Columbia drinking water	surface	NR	NQ (NA)	NR	NR	Scheiman et al., 1974
Carrollton Water Plant in New Orleans, LA[c]	surface	0.03 (NA)	0.10 (NA)	0.10 (NA)	0.64 (NA)	U.S. EPA, 1974; Keith et al., 1976
Jefferson #1 Water Plant in New Orleans, LA[c]	surface	0.03 (NA)	0.36 (NA)	0.46 (NA)	0.83 (NA)	U.S. EPA, 1974; Keith et al., 1976
Jefferson #2 Water Plant in New Orleans, LA[c]	surface	0.01 (NA)	0.23 (NA)	0.27 (NA)	0.73 (NA)	U.S. EPA, 1974; Keith et al., 1976
Cincinnati, OH drinking water	surface	NQ	NQ	NQ	NQ	Kopfler et al., 1975
Miami, FL drinking water	groundwater	1.0 (NA)	5.0 (NA)	30.0 (NA)	NR	U.S. EPA, 1975
Seattle, WA drinking water	surface	0.01 (NA)	0.01 (NA)	ND	NR	U.S. EPA, 1975
Ottumwa, IA drinking water	surface	ND	0.1 (NA)	ND	NR	U.S. EPA, 1975
Philadelphia, PA drinking water	surface	ND	0.05 (NA)	ND	NR	U.S. EPA, 1975
Cincinnati, OH drinking water	surface	0.1 (NA)	ND	ND	NR	U.S. EPA, 1975

[a] Numbers in parentheses are % frequency of occurrence

[b] Maximum detected concentrations

[c] Other phthalates have been detected in these waters

ND = Not detected; NQ = compound detected but not quantified; NR = not reported; NA = not applicable because too few samples were analyzed

TABLE 3-4

Percentage Occurrence of Phthalates by Water Source

	Residential	Commercial	Industrial	Tap Water	Influent
Total number of samples	47	42	21	12	18
Diethyl phthalate	49	36		8	50
Di-n-butyl phthalate	34	43	57	25	67
DEHP/di-n-octyl phthalate	23	38	24	17	22

Levins et al. (1979) also reported tap water concentrations of phthalates for each of the four cities. Diethyl phthalate was detected only in Cincinnati at a concentration of 3.3 μg/ℓ. Di-n-butyl phthalate was detected in Cincinnati at 14.3 an in Hartford at 3.8 μg/ℓ. Butyl benzyl phthalate was not detected in tap water for any of the four cities while DEHP was found in Cincinnati only, at a concentration of 16.5 μg/ℓ.

Phthalate esters are reportedly present in drinking water in other parts of the world. Di-n-butyl phthalate at concentrations up to 1 μg/ℓ has been detected in drinking water in Shizuoka, Japan (Shibuya, 1979). Several esters including di-n-butyl and diethyl phthalate have been identified in several water supplies in England (Fielding et al., 1981; Crathorne et al., 1984; Packham et al., 1981). Morita et al. (1974) identified di-n-butyl and di(2-ethylhexyl) phthalate in Tokyo tap water at mean concentrations of 2.3 and 1.3 μg/ℓ, respectively. Shiraishi et al. (1985) identified di(2-ethylhexyl) phthalate in tap water from Tsukuba, Japan. Tap water from Kitakyushu, Japan, was reported to contain diethyl, di-n-butyl and di(ethylhexyl) phthalates at maximum concentrations of 0.021, 0.24 and 0.24 μg/ℓ, respectively (Akiyama et al., 1980; Shinohara et al., 1981).

On the basis of an overall average phthalate drinking water concentration of 1 μg/ℓ (U.S. EPA, 1975) and a consumption rate of 2 ℓ/day, the daily exposure to phthalate ester by an individual in the United States is ~2 μg.

3.2. AIR

It is difficult to estimate the magnitude of different sources in contributing to the atmospheric level of phthalate esters. Phthalate esters used for nonplasticizer purposes, such as pesticide carriers, cosmetics, fragrances and insect repellant, are subject to direct evaporation and may contribute substantially to the atmospheric burden of these compounds (Peakall, 1975). The release of phthalates into the atmosphere from various plastics used in weather stripping, furniture, auto upholstery, wall coverings and other household materials will add to this. Reportedly, a new room with PVC flooring may contain 0.15-0.26 mg/m³ of phthalates (Peakall, 1975). Kiselev et al. (1983) have shown that the use of certain plastics as household items can result in the release of diethyl, dimethyl, dibutyl and dioctyl phthalates into the atmosphere. Probably the largest amount of atmospheric phthalate esters originate from the incineration of the plastics containing phthalate esters. Peakall (1975) estimated that ~2% of total phthalate-containing plastics used in the United States vaporizes into the atmosphere during incineration. Several investigators have identified phthalate esters in fly ash from municipal incinerators, including dimethyl, diethyl, dibutyl, dioctyl, diisooctyl and n-butyl benzyl phthalates (Tong et al., 1984; Viau et al., 1984; Eiceman et al., 1979, 1981). The concentrations of dimethyl, dibutyl and dioctyl phthalates in the fly ash from an electrostatic precipitater of a coal-fired power station in Fruitland, NM, were reported to be 46 ppb (371 μg/m³), 140 ppb (1620 μg/m³) and 45 ppb (731 μg/m³), respectively (Harrison et al., 1985). Esters including diethyl, diisobutyl, dibutyl and di(2-ethylhexyl) phthalates were identified in the emissions from combination coal/refuse combustion (Vick et al., 1978). Similarly, phthalate esters were identified in the emissions of a wire-reclamation incinerator (Hryhorczuk et al., 1981).

The presence of atmospheric phthalate esters were reported by several investigators (Wauters et al., 1979; Karasek et al., 1978; Meyers and Hites, 1982; Weschler, 1980) and quantitative worldwide levels are presented in Table 3-5. These data for different urban and rural locations are greatly

TABLE 3-5

Atmospheric Levels of a Few Phthalate Esters Measured Throughout the World

Location	Concentrations of Phthalate Esters (mg/m³)			Reference
	DEP	DBP	DEHP	
Chacaltaya, Bolivia (background level)	0.66	28	19	Cautreels et al., 1977
Antwerp, Belgium	4.4	50	70	Cautreels et al., 1977
Atmosphere of Gulf of Mexico	NR	1.30	1.16	Giam et al., 1980
Atmosphere of Gulf of Mexico	NR	0.3	0.4	Giam et al., 1978
Atmosphere of North Atlantic	NR	1.0	2.9	Giam et al., 1978
Barrow, AK	0.2	1.0	~20	Weschler, 1981
Atmosphere of Enewetak Atoll, North Pacific Ocean (background)	NR	0.87	1.4	Atlas and Giam, 1981
College Station, TX	NR	3.8	2.4	Atlas and Giam, 1981
Pigeon Key, FL	NR	18.5	16.6	Atlas and Giam, 1981
New York City, NY	NR	14.2	13.7	Bove et al., 1978
Sterling Forest, NY	NR	1.1	2.8	Bove et al., 1978
Indoor air, Wichita, KS	NR	NR	55	Weschler, 1984
Outdoor air, Wichita, KS	NR	NR	2.2	Weschler, 1984
Indoor air, Lubbock, TX	NR	0.2	20	Weschler, 1984
Outdoor air, Lubbock, TX	NR	0.2	2.0	Weschler, 1984
Hamilton, Ontario, Canada	NR	700*	300*	Thomas, 1973

*These values are much higher because the sampling site was adjacent to a municipal incinerator.

NR = Not reported

varied. For example, the sum of di-n-butyl and di(2-ethylhexyl) phthalate concentrations in New York City was <20 ng/m³ (Bove et al., 1978), while the value for the sum of the same two compounds was ~120 ng/m³ for Antwerp, Belgium (Cautreels, et al., 1977). There is also a large difference in the reported levels of phthalate esters for remote areas and in some cases the phthalate concentrations in remote areas reported by one author exceeds the urban phthalate level reported by another author. Obviously, unless more air monitoring data are developed in the United States, it will not be possible to provide an average urban and rural levels for the phthalate esters. The Great Lakes Science Advisory Board (1980) estimates that a total of ~95 metric tons of airborne di-n-butyl and di(2-ethylhexyl) phthalates are deposited into the Great Lakes every year.

Maximum exposure to phthalate esters is likely to be under occupational conditions. The National Occupational Hazard Survey (NIOSH, 1985) estimates that ~2,406,700 workers are annually exposed to diethyl, di-n-butyl and di(2-ethylhexyl) phthalates in the United States. U.S. EPA (1980a) reported that the concentration of phthalate esters ranged from 1.7-40 mg/m³ in one area and from 10-66 mg/m³ in another area of a company that manufactured artificial leather and PVC films. The level of diethyl phalate in the vulcanization area of a shoe-sole factory was reported to vary between 0 and 120 μg/m³ (Cocheo et al., 1983). Concentrations of di-n-butyl, diisobutyl and di(2-ethylhexyl) phthalate in the vulcanization area of a tire retreading factory were 10-2500, 5-500 and 0-2 μg/m³, respectively (Cocheo et al., 1983).

American published reports on the levels of phthalate esters in occupational atmosphere are rare. The exposure of phthalate esters to the U.S. population residing in urban, suburban and rural areas cannot be estimated because of the lack of reliable monitoring data.

3.3. FOOD

Many of the packaging materials and tubings used to produce foods and beverages are plastics that contain phthalate esters. These esters may migrate from the plastics to the food during contact. Two 1 m PVC tubings, one containing 47.2% dinonyl phthalate and the other containing 5.5% di(2-ethylhexyl) phthalate, when kept in contact with 100 mℓ milk for a period of 24 hours at a temperature of 38°C, leached out 46 and 20 mg/ℓ of the two respective compounds into the milk (Wildbrett, 1973). It is also reported that cheese and lard kept in contact with plastic films for 1 month at 25°C were contaminated with phthalate esters, at concentrations <2 ppm (U.S. EPA, 1980a). Since commercial vegetable oils are often sold in plastic containers, Williams (1973b) analyzed one corn oil and several soy oil samples for di(2-ethylhexyl) phthalate, but did not detect it in any of these oils. Several authors have identified phthalate esters in foods, particularly aquatic foods; levels and their food sources are given in Table 3-6.

It is evident that phthalate esters are present in a variety of foods consumed by humans. Estimates, however, of human consumption of these compounds from foods requires the foreknowledge of phthalate levels in such foods. In the absence of such data, it is not possible to estimate the phthalate exposure from food sources.

3.4. DERMAL

Phthalate esters can be absorbed through the skin during the use of many cosmetic products, insect repellants and the water from PVC-lined swimming pools. Hemodialysis tubing and PVC bags containing intravenous solutions also can be sources of exposure to these compounds for a special segment of the population. U.S. EPA (1980a) describes phthalate ester exposure from

TABLE 3-6

Concentrations of Phthalate Esters in Some Foods

Food	Source	Concentration of Phthalate (mg/kg)		Reference
		DBP	DEHP	
Perch (*Perca fluviatilis*) muscle	South Coast of Finland	NR	0-0.1	Persson et al., 1978
Pike (*Esox hicius*) muscle	South Coast of Finland	NR	0	Persson et al., 1978
Clams	Portland, ME	0.07	0.14	Ray et al., 1983
Herring (fillets)	Gulf of St. Lawrence	NR	4.71	Musial et al., 1981
Mackerel (fillets)	Gulf of St. Lawrence	NR	6.50	Musial et al., 1981
Plaice (fillets)	Gulf of St. Lawrence	NR	<0.010	Musial et al., 1981
Redfish (fillets)	Gulf of St. Lawrence	NR	<0.010	Musial et al., 1981
Spade fish (muscle)	Gulf of Mexico	NR	0.011	Giam et al., 1975
Croaker (muscle)	Gulf of Mexico	NR	0.003	Giam et al., 1975
Trout (muscle)	Gulf of Mexico	NR	0.004	Giam et al., 1975
Shark (muscle)	Gulf of Mexico	NR	0.002	Giam et al., 1975
Catfish (muscle)	Gulf of Mexico	NR	ND	Giam et al., 1975
Shrimp (whole)	Gulf of Mexico	NR	0.008	Giam et al., 1975
Sting ray (muscle)	Gulf of Mexico	NR	0.012	Giam et al., 1975
Eel (whole)	Gulf of Mexico	NR	0.002	Giam et al., 1975
Blue crab (muscle)	Gulf of Mexico	NR	0.003	Giam et al., 1975
Rainbow trout (whole)	Tokoyo, Japan	0.6	NR	Morita et al., 1973
Whole milk	Tokoyo, Japan	0.05	NR	Morita et al., 1973
Skim milk	Tokoyo, Japan	0.2	NR	Morita et al., 1973
Butter	Tokoyo, Japan	4-11	NR	Morita et al., 1973
Bourbon whiskey	Imported to Japan	0.06	NR	Saito et al., 1980
Unprocessed eel	Canada	ND	0.104	Williams, 1973a
Unprocessed catfish	Lake St. Pierre	ND	NQ	Williams, 1973a
Unprocessed pickerel	Lake Huron	ND	NQ	Williams, 1973a
Unprocessed pickerel	Lake Ontario	NQ	NQ	Williams, 1973a
Canned tuna[a]	Canada	0.078	0.160	Williams, 1973a
Canned salmon	Canada	0.037	0.089	Williams, 1973a
Canned shrimp	Canada	NQ	ND	Williams, 1973a

TABLE 3-6 (cont.)

Food	Source	Concentration of Phthalate (mg/kg)		Reference
		DBP	DEHP	
Frozen rainbow trout	Canada	ND	NQ	Williams, 1973a
Frozen ocean perch	Canada	ND	NQ	Williams, 1973a
Frozen mackerel	Canada	ND	NQ	Williams, 1973a
Hatchery-reared juvenile Atlantic salmon (commercial)	Atlantic Ocean	NR	13-16[b]	Zitko, 1973
Egg white	Japan	0.098	0.182	Ishida et al., 1981
Salad oil[a]	Japan	0.11	0.15	Tomita et al., 1977
Lard	Japan	0.09	0.10	Tomita et al., 1977
Soft margarine[a]	Japan	3.12	0.21	Tomita et al., 1977
Mayonnaise[a]	Japan	1.25	0.65	Tomita et al., 1977
Instant vegetable cream soup	Japan	6.35	ND	Tomita et al., 1977
Instant corn cream soup	Japan	0.17	ND	Tomita et al., 1977
Fried cake	Japan	0.64	0.49	Tomita et al., 1977
Wheat flour[a]	Japan	2.47	1.57	Tomita et al., 1977
Bread crumbs[a]	Japan	0.77	0.03	Tomita et al., 1977
Rice powder	Japan	0.03	0.33	Tomita et al., 1977
Mashed potatoes	Japan	0.09	0.05	Tomita et al., 1977
Sugar	Japan	0.16	0.01	Tomita et al., 1977
Table salt[a]	Japan	1.41	0.04	Tomita et al., 1977
Soy sauce[a]	Japan	0.03	0.07	Tomita et al., 1977
Worchestershire sauce[a]	Japan	0.17	0.08	Tomita et al., 1977
Honey	Japan	0.11	0.17	Tomita et al., 1977
Pickles	Japan	0.16	0.37	Tomita et al., 1977
Rainbow trout	Great Lakes	5.4	NR	Glass et al., 1977
Long-nose sucker	Great Lakes	8.1	NR	Glass et al., 1977
Whitefish (fillet)	Great Lakes	NR	2.2	Glass et al., 1977

[a] These are the highest reported values

[b] This represents concentration range in the lipid

NR = Not reported; NQ = compound identified but not quantified; ND = not detected other medical sources. Several authors have measured the levels of phthalate esters in serum from surgical patients (Ching et al., 1981) and in human adipose tissues (Mes and Campbell, 1976; Mes et al., 1974), although the latter concentrations probably represent exposure from inhalation, ingestion and dermal exposure sources.

3.5. SUMMARY

Phthalate esters are ubiquitous in the environment. They have been identified in surface waters in the United States and elsewhere in the world. The maximum reported concentration of di(2-ethylhexyl) phthalate in any surface water was 600 μg/ℓ, which was detected in Mississippi River water (Corcoran, 1973). The average concentration of individual phthalate esters in surface water is <1 μg/ℓ (Michael et al., 1984). Phthalate esters have also been identified in groundwater from contaminated sites; a maximum of 100 μg/ℓ of di(2-ethylhexyl) phthalate was detected in groundwater from a landfill site in New Castle County, DE (DeWalle and Chian, 1981). Several phthalate esters have been identified in drinking water abstracted both from surface water and groundwater. The maximum concentrations of diethyl, di-n-butyl, di(2-ethylhexyl) and butyl benzyl phthalates in 39 public water wells were reported to 4.6, 470, 170 and 38 μg/ℓ, respectively (CEQ, 1980, 1981; Burmaster, 1982). The Science Advisory Board of the U.S. EPA reviewed selected organic chemicals and estimated that the distribution of the phthalate esters is ~50% in U.S. drinking waters, with an overall phthalate concentration of ~1 μg/ℓ (U.S. EPA, 1978c). On the basis of these data and an average consumption rate of 2 ℓ/day, daily phthalate exposure to a U.S. individual from ingesting drinking water is estimated to be 2 μg.

Phthalate esters have been detected in ambient atmosphere. Probably the biggest contributor to atmospheric phthalate is the incineration of plastics that contained the esters (Peakall, 1975). The concentrations of di-n-butyl and di(2-ethylhexyl) phthalate in New York City's ambient air were 4.2 mg/m^3 and 13.7 ng/m^3, respectively (Bove et al., 1978). In College Station, TX, the corresponding values were reported to be 3.8 and 2.4 ng/m^3 (Atlas and Giam, 1981). Until more air monitoring data become available, it is not possible to provide average urban and rural levels of phthalate esters. Consequently, inhalation exposure of phthalate esters to the U.S. population residing in urban, suburban and rural areas cannot be estimated. Maximum exposure to phthalate esters is likely to occur under occupational conditions. Concentrations of phthalate esters ranged from 1.7-40 mg/m^3 in a mixing area and from 10-66 mg/m^3 in another area of a company manufacturing artificial leather and films of PVC (U.S. EPA, 1980b). NIOSH (1985) estimates that ~2,406,700 workers are annually exposed to diethyl, di-n-butyl and di(2-ethylhexyl) phthalate in the United States.

Several authors have identified phthalate esters in foods. Di(2-ethylhexyl) phthalate was detected at a concentration of 6.50 mg/kg in mackerel fillets (Musial et al., 1981). The concentration of di-n-butyl phthalate in rainbow trout from the Great Lakes was reported to be 8.1 mg/kg (Glass et al., 1977). In butter samples obtained from Japan, the concentration of di-n-butyl phthalate was 4-11 mg/kg (Morita et al., 1973). Instant vegetable cream soup obtained from a Japanese market contained 6.35 mg/kg of di-n-butyl phthalate (Tomita et al., 1977). No estimates of phthalate ester exposure from food composites typically consumed by an individual in the United States are available.

Phthalate esters can be absorbed through the skin during the use of many cosmetic products, insect repellants and the water from PVC-lined swimming pools (U.S. EPA, 1980a). A special segment of the population is exposed to phthalate esters during medical/surgical procedures, such as hemodialysis and intravenous applications. No estimates on the dermal exposure of phthalate esters to individuals can be made from the data available in the literature as cited in the Appendix.

4. PHARMACOKINETICS

The pharmacokinetics of phthalate esters has been reviewed by Kluwe (1982), Albro et al. (1982), Thomas and Thomas (1984), and U.S. EPA (1978b, 1980b, 1985a). The majority of studies have focused on di(2-ethylhexyl) phthalate. Information on the pharmacokinetics of aryl or aryl/alkyl esters of phthalic acid could not be located in the available literature as cited in the Appendix.

4.1. ABSORPTION

In general, excretion profiles indicate that alkyl phthalic acid esters and their degradation products are probably well absorbed from the gastrointestinal tract.

When di(2-ethylhexyl) phthalate (10 or 2000 ppm) was administered to rats in the diet, >90% of the administered dose was excreted as metabolites in the urine; the remainder was excreted in the feces (Williams and Blanchfield, 1974). When di(2-ethylhexyl) phthalate was administered to rats by gavage (3 or 1000 mg/kg, vehicle = corn oil), 42-54% of the administered dose was excreted as metabolites in the urine, while 24-57% was excreted as metabolites in the feces within 1-4 days (Williams and Blanchfield, 1974; Daniel and Bratt, 1974). In humans, 10-15% of a single oral dose of di(2-ethylhexyl) phthalate was excreted in the urine within 24 hours of administration (Schmid and Schlatter, 1985). Absorption of di(2-ethylhexyl) phthalate and degradation products may be greater than urinary levels of metabolites would indicate, since substantial biliary excretion has been observed in rats, dogs and miniature pigs (Daniel and Bratt, 1974; Ikeda et al., 1980).

Gastrointestinal absorption of di-n-butyl phthalate can be inferred from observations that >90% of a single dose of di-n-butyl phthalate administered to rats by gavage (60, 270 or 2310 mg/kg, vehicles = corn oil, DMSO) was excreted as metabolites in the urine within 2 days; the remainder was excreted in the feces (Tanaka et al., 1978; Williams and Blanchfield, 1975). Substantial biliary excretion of di-n-butyl phthalate metabolites (30-60% of 60 mg/kg dose within 2 days) was also observed (Tanaka et al., 1978).

Ikeda et al. (1978) observed that metabolites of diisooctyl phthalate were excreted in the urine, feces and bile of dogs, rats and miniature pigs exposed orally to diisooctyl phthalate (21-28 days in feed, then single gavage dose of ^{14}C-diisooctyl phthalate in corn oil), qualitatively indicating that gastrointestinal absorption of diisooctyl phthalate or its degradation products occurs in each of these species.

Apparent hydrolytic activity toward di(2-ethylhexyl) phthalate in pancreatic homogenates led Albro and Thomas (1973) to hypothesize that very little, if any, intact phthalate diester is absorbed from the gastrointestinal tract. Further studies have shown that phthalate esters di(2-ethylhexyl) phthalate, dimethyl phthalate, di-n-butyl phthalate, di-n-octyl phthalate) are readily hydrolized to their monoester derivatives by enzymes in intestinal mucosal cells (Rowland, 1974; White et al., 1980) and other tissues (Carter et al., 1974), and by extracellular enzymes present in the intestinal contents of rats, ferrets and baboons (Rowland, 1974; Rowland et al., 1977; Lake et al., 1977b).

Recent gavage studies on rats demonstrated that di(2-ethylhexyl) phthalate was hydrolyzed to monoethylhexyl phthalate, which was subsequently absorbed (Teirlynck and Belpaire, 1985; Oishi and Hiraga, 1982). Teirlynck and Belpaire (1985) reported that plasma concentrations of 8.8±1.7 μg/mℓ di(2-ethylhexyl) phthalate and 63.2±8.7 μg/mℓ monoethylhexyl phthalate were reached within 3 hours after a single oral dose of di(2-ethylhexyl) phthalate (2.8 g/kg in corn oil). These observations raise concern about the validity of using route-to-route extrapolation in either quantitative or qualitative assessment of risk associated with ingestion, since it appears that the dialkyl esters are largely hydrolyzed to monoester derivatives before absorption from the gastrointestinal tract. In a recent study on rats, Pollack et al. (1985a) found that 80% of a single oral (gavage in corn oil) dose of di(2-ethylhexyl) phthalate was hydrolyzed to its monoester derivative (monoethylhexyl phthalate) and subsequently absorbed; 13% of the dose was absorbed as di(2-ethylhexyl) phthalate. The ratio of the AUCs for monoethylhexyl phthalate to di(2-ethylhexyl) phthalate was ~7. Repetitive oral dosing did not affect the extent of absorption. In contrast, uptake of di(2-ethylhexyl) phthalate and its derivative(s) into the bloodstream from the peritoneal cavity was poor. Only 1% of an equivalent intraperitoneal dose was hydrolyzed to monoethylhexyl phthalate; 5.2% was taken up as di(2-ethylhexyl) phthalate. The ratio of the AUC for monoethylhexyl phthalate to di(2-ethylhexyl) phthalate after either intraperitoneal or intra-arterial administration was <0.4. Furthermore, repetitive intraperitoneal administration of di(2-ethylhexyl) phthalate led to an apparent decrease in the rate and extent of uptake. Poor intraperitoneal uptake into the blood was attributed to the fact that di(2-ethylhexyl) phthalate is lipophilic and distributed into the peritoneal fat. U.S. EPA (1980b) and Thomas and Thomas (1984) state that phthalic acid esters may not be readily taken into the bloodstream from the peritoneal cavity, and both sources question whether intraperitoneal studies are useful in oral risk assessment.

4.2. DISTRIBUTION

Several studies have shown that di(2-ethylhexyl) phthalate and di-n-butyl phthalate, administered either orally or intravenously, are cleared rapidly from the body, largely within 24 hours of exposure (Tanaka et al., 1975, 1978; Williams and Blanchfield, 1974, 1975; Ikeda et al., 1980; Daniel and Bratt, 1974; Oishi and Hiraga, 1982; Teirlynck and Belpaire, 1985). The same observation holds true for orally administered diisooctyl phthalate (Ikeda, et al., 1978). The parent compound and metabolites are distributed primarily to plasma, liver, kidney, the gastrointestinal tract and fat. Metabolites have also been found in almost every other tissue. In particular, a high concentration of monoethylhexyl phthalate, the hydrolytic derivative of di(2-ethylhexyl) phthalate, has been found in the testes of rats (Oishi and Hiraga, 1982). Concentrations of di(2-ethylhexyl) phthalate and metabolites in various tissues, particularly liver, kidney and fat, vary with route of administration (diet, gavage, parenteral), vehicle and dose (Thomas and Thomas, 1984; Pollack et al., 1985a; Albro et al., 1982).

In a dietary study on rats, Daniel and Bratt (1974) reported that steady-state tissue concentrations of radioactivity from ^{14}C-di(2-ethylhexyl) phthalate were proportional to dietary concentrations and reached maximum values in liver and fat within 1 and 2 weeks of treatment, respectively. When dietary di(2-ethylhexyl) phthalate was removed, radioactivity in the liver and fat declined, with half-lives of 1-2 days and 3-5 days, respectively.

The distribution and retention of di(2-ethylhexyl) phthalate and its monoester derivative, monoethylhexyl phthalate, were examined in gavage studies on rats. Teirlynck and Belpaire (1985) reported that maximum concentrations of monoethylhexyl phthalate and di(2-ethylhexyl) phthalate were reached in the plasma within 3 hours of a single dose of di(2-ethylhexyl) phthalate (2.8 g/kg in corn oil). The ratio of the AUCs for monoethylhexyl phthalate to di(2-ethylhexyl) phthalate was 16.1±6.1. Monoethylhexyl phthalate disappeared from the plasma with a $t_{1/2}$ of 5.2±0.5 hours. The concentration of di(2-ethylhexyl) phthalate in the plasma was considered too low for accurate estimation of $t_{1/2}$. Repetitive dosing with di(2-ethylhexyl) phthalate (2.8 g/kg/day in corn oil for 7 days) produced no accumulation of either monoethylhexyl phthalate or di(2-ethylhexyl) phthalate in the plasma.

Oishi and Hiraga (1982) reported that maximum concentrations of di(2-ethylhexyl) phthalate and monoethylhexyl phthalate were observed in the blood and tissues of rats within 6-24 hours after a single oral dose of di(2-ethylhexyl) phthalate of 25 mmol/kg (9.8 g/kg) in corn oil. In general, the disappearance of monoethylhexyl phthalate from the tissues was slower than that of di(2-ethylhexyl) phthalate; half-lives for monoethylhexyl phthalate ranged from 22.6-68 hours, while half-lives for di(2-ethylhexyl) phthalate in several tissues ranged from 1.49-156 hours (Table 4-1). The ratio of monoethylhexyl phthalate/di(2-ethylhexyl) phthalate, measured 6 hours after dosing, was 113±23, 79±17, 210±4.8, 46±0.57 and 87±24 in blood, liver, testes, heart and epididymal fat, respectively. In this study, concentrations of di(2-ethylhexyl) phthalate and monoethylhexyl phthalate in the kidneys were very low.

Little is known about the ability of phthalic acid esters to cross the placenta (Kluwe, 1982). Using perfusion techniques, Kihlstrom (1983) showed that intravenously administered di(2-ethylhexyl) phthalate is transported across the placenta of guinea pigs and appears in the fetal circulation.

TABLE 4-1

Biological Half-Lives of Di(2-ethylhexyl) Phthalate and Monoethylhexyl Phthalate in Rats After a Single Oral Dose of Di(2-ethylhexyl) Phthalate (25 mmol/kg in Corn Oil)[a]

Tissue	$t_{1/2}$ (hours)[b]	
	MEHP	DEHP
Blood	23.8	18.6
Liver	31.9	28.4
Testes	49.9 ($6 < t < 48$)	8.28 ($24 < t < 96$)
Heart	28.8	15.2
Spleen	22.6	ND
Lung	ND	1.49 ($1 < t < 6$) 25.3 ($6 < t < 96$)
Epididymal fat	67.6 ($24 < t < 96$)	156 ($48 < t < 96$)

[a] Source: Oishi and Hiraga, 1982

[b] Biological $t_{1/2}$ calculated from least-squares fit of data during 6-96 hours except for timeframes indicated for testes, lung and fat.

ND = No data

Singh et al. (1975) demonstrated that radioactivity from ^{14}C-diethyl phthalate and ^{14}C-di(2-ethylhexyl) phthalate (position of label not reported) administered intraperitoneally to rats on either day 5 or 10 of gestation was found in the placentas, amniotic fluid and fetal tissue throughout gestation. The relevance of these findings to orally ingested phthalic acid esters is unclear.

4.3. METABOLISM

Kluwe et al. (1982a) states that, in general, the metabolism of alkyl phthalic acid esters is not qualitatively affected by route of administration. The first step of metabolism entails hydrolysis to a monoester derivative (Kluwe, 1982); the location and extent to which this occurs is route-dependent (Pollack et al., 1985a). Ingested phthalic acid esters are converted to their monoester derivatives by enzymes in the gastrointestinal tract before absorption (see Section 4.1.). Since other tissues contain enzymes capable of hydrolyzing phthalic acid esters (Carter et al., 1974), parenterally administered phthalic acid esters can also be hydrolyzed.

Once formed, the monoester derivative can then be further hydrolyzed to phthalic acid and excreted; conjugated to glucuronide and excreted; or oxidized and excreted (Kluwe, 1982).

Short-chain phthalic acid esters, such as di-n-butyl phthalate and dimethyl phthalate can be excreted as parent compound, their monoester derivatives and pthalic acid. In rats, only small quantities of monoester derivatives from longer-chain phthalic acid esters, such as di(2-ethylhexyl) phthalate or diisooctyl phthalate are converted to phthalic acid before excretion (Albro and Thomas, 1973; Albro and Moore, 1974; Albro et al., 1973).

In all mammalian species tested but the rat, glucuronide conjugates of monoethylhexyl phthalate are the major urinary metabolites of di(2-ethylhexyl) phthalate (Albro et al., 1982; Kluwe, 1982). Species that form glucuronide conjugates of monoethylhexyl phthalate include humans, hamsters, green monkeys, guinea pigs and mice (Albro et al., 1981, 1982; Peck et al., 1978; Teirlynck and Belpaire, 1985; Schmid and Schlatter, 1985). The absence of conjugates of di(2-ethylhexyl) phthalate metabolites has been confirmed in 3 strains of rat (Williams and Blanchfield, 1975; Daniel and Bratt, 1974; Chu et al., 1981; Tanaka et al., 1975; Albro and Moore, 1974; Albro et al., 1973; Albro et al., 1982; Kluwe, 1982; Thomas and Thomas, 1984). In contrast, a glucuronide conjugate of the di-n-butyl phthalate monoester derivative (mono-butyl phthalate) has been identified as a major urinary metabolite in rats, in hamsters and guinea pigs (Tanaka et al., 1978; Foster et al., 1982; Kaneshima et al., 1978).

Oxidation of monoester derivatives of dialkyl phthalic acid esters has been observed in rats, guinea pigs and hamsters (Williams and Blanchfield, 1974, 1975; Tanaka et al., 1978; Daniel and Bratt, 1974; Chu et al., 1981; Lhuguenot et al., 1985). In general, the terminal or next-to-last carbon atom in the monoester derivative is oxidized to an alcohol. Aldehydes, ketones and carboxylic acids are formed by successive oxidations. Compounds with alkyl chains containing six or more linear carbons may undergo β-oxidation (Kluwe, 1982; Albro and Moore, 1974; Albro et al., 1973).

4.4. EXCRETION

Excretion of diisooctyl phthalate, di-n-butyl phthalate and di(2-ethylhexyl) phthalate and their metabolites has been studied. Routes of excretion for these compounds include urine, feces and bile; the relative importance of route of excretion depends upon the compound and species, while the rate of excretion appears to be rapid despite those considerations. The available studies are summarized in Table 4-2.

Half-lives of 7.9 and 12 hours have been reported for excretion of di(2-ethylhexyl) phthalate and metabolites in rats (Teirlynck and Belpaire, 1985) and humans (Schmid and Schlaffer, 1985), respectively. Excretion half-lives of 1.2 and 5.4 hours have been reported for diisooctyl phthalate and metabolites in dogs and miniature pigs, respectively (Ikeda et al., 1978).

Comparative studies with ^{14}C-diisooctyl phthalate (Ikeda et al., 1978) have shown that urinary excretion prevails in minipigs, fecal excretion prevails in dogs, and rats excrete approximately equal quantities of radioactivity in urine and feces. Early biliary excretion (4-24 hours after dosing) was shown to be substantial in dogs, but low in rats and minipigs.

In rats, di-n-butyl phthalate is primarily excreted in the urine (~90%), with the balance excreted in the feces (Tanaka et al., 1978; Williams and Blanchfield, 1975). Substantial biliary excretion has been shown to occur from within a few hours to 5 days after dosing (Tanaka et al., 1978; Kaneshima et al., 1978).

It is difficult to generalize about patterns of excretion of di(2-ethylhexyl) phthalate in rats, althrough the reasons for apparent discrepancies are unclear. In a recent comparative study where rats, dogs and minipigs were fed a diet containing di(2-ethylhexyl) phthalate (equivalent to 50 mg/kg/day) for 21-28 days then treated by gavage with a single dose of ^{14}C-di(2-ethylhexyl) phthalate (50 mg/kg), urinary excretion was the major route in minipigs only. Rats and dogs, in particular, excreted radioactivity primarily in the feces. Biliary excretion was shown to be substantial in dogs and minimal in minipigs and rats (Ikeda et al., 1980).

TABLE 4-2

Excretion of Phthalic Acid Esters

Compound	Species	$t_{1/2}$ (hours)	Route[a]	Time	% Dose			Reference
					Urine	Feces	Bile	
DEHP	human	12	oral (single dose)	2 days	10-15	NR	NR	Schmid and Schlatter, 1985
	human	NR	oral (4 doses)	2 days	10-25	NR	NR	Schmid and Schlatter, 1985
	rat	7.9	gavage	72 hours	19.3	balance	NR	Teirlynck and Belpaire, 1985
	rat	NR	gavage	48-192 hours	~60	~40	NR	Williams and Blanchfield, 1974
	rat	NR	diet or gavage	48 hours	42-57	38-57	9-14	Daniel and Bratt, 1974
	rat	NR	diet/gavage[b]	4 days	27-37	53-56	<1	Ikeda et al., 1980
	rat	NR	diet	NR	91-98	2-8	NR	Williams and Blanchfield, 1974
	rat	NR	i.v.	7 days	49	28	NR	Tanaka et al., 1975
	dog	NR	diet/gavage[b]	4 days	12-21	55-75	7-10	Ikeda et al., 1980
	minipig	NR	diet/gavage[b]	4 days	79	26	0.01-1.2	Ikeda et al., 1980
DBP	rat	NR	gavage or i.v.	48 hours	≥90	~8	32-57 (gavage only)	Tanaka et al., 1978
	rat	NR	gavage	48 hours	80-90	balance	NR	Williams and Blanchfield, 1975
	rat	NR	gavage	5 hours	NR	NR	4.5	Kaneshima et al., 1978
	rat	NR	i.v.	5 hours	NR	NR	10	Kaneshima et al., 1978
DIOP	rat	NR	diet/gavage[b]	4 days	41-57	38-45	<1	Ikeda et al., 1978
	dog	1.2	diet/gavage[b]	4-21 days	23-28	69-80	trace-0.29	Ikeda et al., 1978
	dog	1.2	diet/gavage[b]	4-24 hours	9	41	6-13	Ikeda et al., 1978
	minipig	5.4	diet/gavage[b]	4-21 days	65-86	13-32	trace-0.01	Ikeda et al., 1978
	minipig	5.4	diet/gavage[b]	4-24 hours	15-49	0-0.13	0.25-0.73	Ikeda et al., 1978

[a] Vehicle = corn oil for gavage studies

[b] Dietary administration for 21-28 days, fasted overnight, then by gavage with ^{14}C-Ester in corn oil.

NR = Not reported

Daniel and Bratt (1974) observed substantial biliary excretion (9-14%) in rats when di(2-ethylhexyl) phthalate was administered in the diet for 7 days or as a single dose by gavage. The dose of di(2-ethylhexyl) phthalate (2.6 mg/kg bw) was considerably lower than the dose applied by Ikeda et al. (1980) (50 mg/kg bw). The reason for the discrepancy remains unclear.

Other oral studies (gavage and diet) on rats indicate that either fecal and urinary excretion are approximately equal (Williams and Blanchfield, 1974; Daniel and Bratt, 1974) or that fecal excretion prevails (Teirlynck and Belpaire, 1985). In a dietary study on rats, Williams and Blanchfield (1974) showed that regardless of concentration [10 or 2000 ppm di(2-ethylhexyl) phthalate], urinary excretion prevailed (91-98% of administered dose). In humans, only 10-15% of a single oral dose or 10-25% of four daily oral doses of di(2-ethylhexyl) phthalate were recovered as metabolites in the urine within 48 hours of administration (Schmid and Schlatter, 1985).

4.5. SUMMARY

Oral studies show that di(2-ethylhexyl) phthalate, di-n-butyl phthalate, and diisooctyl phthalate are absorbed from the gastrointestinal tract (Williams and Blanchfield, 1974, 1975; Daniel and Bratt, 1974; Ikeda et al., 1978, 1980; Tanaka et al., 1978; Pollack et al., 1985a; Oishi and Hiraga, 1982; Teirlynck and Belpaire, 1985; Schmid and Schlatter, 1985). Pollack et al. (1985a) demonstrated that uptake of intraperitoneally administered di(2-ethylhexyl) phthalate into the blood is poor in rats. Orally administered phthalic acid esters are primarily and largely converted to their monoester derivatives by enzymes in the gastrointestinal tract before absorption (Albro and Thomas, 1973; Rowland, 1974; Rowland et al., 1977; Lake et al., 1977; Carter et al., 1974; White et al., 1980; Pollack et al., 1985; Teirlynck and Belpaire, 1985; Oishi and Hiroga, 1982). Other tissues such as the liver have also been shown to hydrolyze phthalic acid esters (Carter et al., 1974). In contrast, intraperitoneally administered di(2-ethylhexyl) phthalate is taken up primarily as di(2-ethylhexyl) phthalate, with only 1% hydrolyzed to monoethylhexyl phthalate (Pollack et al., 1985a).

Oral and intravenous studies indicate that di(2-ethylhexyl) phthalate, di-n-butyl phthalate and diisooctyl phthalate are not retained for long in the body (Tanaka et al., 1975, 1978; Williams and Blanchfield, 1974, 1975; Daniel and Bratt, 1974; Oishi and Hiraga, 1982; Teirlynck and Belpaire, 1985; Ikeda et al., 1978, 1980). In general, phthalic acid esters and metabolites distribute primarily to liver, kidneys, fat and the gastrointestinal tract. Metabolites have been found in almost every tissue; in particular a high concentration of monoethylhexyl phthalate, the hydrolytic derivative of di(2-ethylhexyl) phthalate, has been observed in the testes of rats (Oishi and Hiraga, 1982). The distribution of di(2-ethylhexyl) phthalate and metabolites in various tissues, particularly liver, kidneys and fat, has been observed to vary with route of administration (diet, gavage, parenteral), vehicle and dose (Thomas and Thomas, 1984; Pollack et al., 1985a; Albro et al., 1982). In a dietary study on rats, radioactivity from ^{14}C-di(2-ethylhexyl) phthalate in the liver and fat declined with half-lives of 1-2 and 3-5 days, respectively (Daniel and Bratt, 1974). In gavage studies (Oishi and Hiraga, 1982), the disappearance of di(2-ethylhexyl) phthalate from tissues ($t_{1/2}$ ranging from 1.49-156 hours) was more rapid than for that of monoethylhexyl phthalate ($t_{1/2}$ ranging from 22.6-68 hours).

Although short-chain phthalic acid diesters such as dimethyl phthalate can be excreted unchanged in the urine, most phthalic acid diesters are further metabolized before excretion. The first step of metabolism entails hydrolysis of the parent compound to a monoester derivative. Once formed, the monoester derivative can then be further hydrolyzed to phthalic acid and excreted, conjugated with glucuronide then excreted, or oxidized and excreted. The first alternative occurs primarily with short-chain phthalic acid esters (Albro and Thomas, 1973; Albro and Moore, 1974; Albro et al., 1973). The second alternative is the primary route of metabolism for di(2-ethylhexyl) phthalate and occurs in all species except the rat (Albro et al., 1973, 1981, 1982; Kluwe et al., 1982a,b; Peck et al., 1978; Teirlynck and Belpaire, 1985; Schmid and Schlatter, 1985; Williams and Blanchfield, 1975; Daniel and Bratt, 1974; Chu et al., 1978; Tanaka et al., 1975; Thomas and Thomas, 1984); however, glucuronide conjugates of di-n-butyl phthalate have been observed in rats (Tanaka et al., 1978; Foster et al., 1982; Kaneshima et al., 1978). The third route of metabolism has been observed in rats, guinea pigs and hamsters (Williams and Blanchfield, 1974, 1975; Tanaka et al., 1978; Daniel and Bratt, 1974; Chu et al., 1981; Shuguenot et al., 1975). The metabolism of phthalic acid esters is not qualitatively affected by route of exposure (Kluwe, 1982).

Excretion of diisooctyl phthalate, di-n-butyl phthalate and di(2-ethylhexyl) phthalates has been studied (Ikeda et al., 1978, 1980; Schmid and Schlatter, 1985; Teirlynck and Belpaire, 1985; Williams and Blanchfield, 1974, 1975; Daniel and Bratt, 1974; Kaneshima et al., 1978; Tanaka et al., 1975, 1978). These compounds and their metabolites are excreted in urine, bile and feces; the relative importance of the route of excretion depends upon the compound and species, while the rate of excretion appears to be rapid. Half-lives of 7.9 and 12 hours were reported for urinary excretion of di(2-ethylhexyl) phthalate in humans and rats, respectively (Schmid and Shlatter, 1985; Teirlynck and Belpaire, 1985). Pharmacokinetic data on aryl or aryl/alkyl pthalates could not be located in the available literature as cited in the Appendix.

5. EFFECTS

5.1. CARCINOGENICITY

Di(2-ethylhexyl) and n-butyl benzyl phthalates have been tested for oncogenicity in NTP-directed feeding studies on rats and mice. Wilbourn and Montesano (1982) reviewed other studies on di(2-ethylhexyl), n-butyl benzyl and di-n-butyl phthalates, which were conducted before the NTP bioassays, and concluded that they were insufficient to assess the carcinogenic potential of phthalate esters because of design and reporting limitations; U.S. EPA (1985a) concurred with this assessment. These studies are listed in Table 5-1. The NTP studies, though not flawless, provide the only reasonable tests of oncogenicity, and are reported as follows.

5.1.1. n-Butyl Benzyl Phthlate. n-Butyl benzyl phthalate (0, 6000 or 12,000 ppm) was fed to groups of 50 male and 50 female F344/N rats and 50 male and 50 female B6C3F1 mice for 28 weeks (male rats only) or 103 weeks (mice and female rats) (NTP, 1982a). Control mice and female rats were killed after 106 weeks on test. Because of high mortality, high-dose male rats and male controls were killed after 29 weeks on test. Male and female mice and female rats exposed to n-butyl benzyl phthalate were killed after 104-106 weeks. Endpoints monitored include body weight, food consumption, mortality, clinical signs of toxicity, and gross and microscopic pathology. When treated animals were compared with controls, a number of compound-related effects were observed. Increased mortality associated with "unexplained internal hemorrhaging" was observed in n-butyl benzyl phthalate-exposed male rats beginning at the 14th week of exposure. Consequently, the study on male rats was terminated after week 28 of exposure.

TABLE 5-1

Inadequate Cancer Studies

Species	Compound	Route	Reference
Rats, dogs, guinea pigs	DEHP	oral (diet)	Carpenter et al., 1953
Rats	DEHP	oral (diet)	Harris et al., 1955
Mice	DEHP	intraperitoneal	Omori, 1976
Mice	BBP	intraperitoneal	Theiss et al., 1977
Rats	BBP	NR	Anonymous, 1968
Mice	DBP	intraperitoneal	Omori, 1976

NR = Not reported

Survival curves were comparable for treated and control mice and female rats. Reduced body weights were observed in all rats and mice fed n-butyl benzyl phthalate. The reduction was slight in female rats but substantial in male and female mice. Food consumption was reduced 70-80% in treated female rats, but data on food consumption were not reported for mice and male rats. A statistically significant increase (p=0.011, Fisher Exact test) in mononuclear cell leukemia was observed in high-dose female rats (Table 5-2) and was frequently accompanied by splenomegaly and hepatomegaly. A statistically significant increase in leukemia or lymphoma was also observed in high-dose female rats (p=0.007, Fisher Exact test). No other compound-related increases in neoplastic or nonneoplastic lesions were observed in female rats. The study on male rats was too brief to provide meaningful analysis of the data. No compound-related increases in the incidences of neoplastic or nonneoplastic lesions were observed in mice of either sex. Dose-related and significant decreases in mammary gland adenomas (female rats), alveolar/bronchiolar adenomas or carcinomas (male mice), lymphomas (male mice), and lymphomas or leukemia (male mice) were observed (see Table 5-2).

NTP (1982a) concluded that n-butyl benzyl phthalate was "probably carcinogenic for female F344/N rats." In a separate report, Kluwe et al. (1982a), however, concluded that since the background incidence of myelomonocytic leukemia is normally high in F344/N rats (8-15% and 9-24% in females and males, respectively), results presented in NTP (1982a) provide only equivocal evidence of n-butyl benzyl phthalate-induced cancer in female rats. Furthermore, the fact that significant and dose-related decreases in incidences of malignant lymphoma, all lymphoma, and lymphoma or leukemia were observed in male mice contributes to the uncertainty that n-butyl

TABLE 5-2

Hematopoietic Neoplasms in F344/N Rats and B6C3F1 Mice Fed n-Butyl Benzyl Phthalate in the Diet for 103 Weeks[a]

Species	Sex	Tumor Type	Incidence (p-value)[b]		
			Control	Low Dose (6000 ppm)	High Dose (12,000 ppm)
Rat	F	mononuclear cell leukemia	7/49 (0.006)	7/49 (NS)	18/50 (0.011)
		leukemia or lymphoma	7/49 (0.004)	7/49 (NS)	19/50 (0.007)
Mouse	M	malignant lymphoma	12/50 (0.024N)[c]	10/49 (NS)	4/50 (0.027N)[c]
		all lymphomas	13/50 (0.015N)[c]	11/49 (NS)	4/50 (0.016N)[c]
		lymphomas or leukemia	14/50 (0.008N)[c]	11/49 (NS)	4/50 (0.009N)[c]
	F	malignant lymphoma	15/50 (NS)	14/50 (NS)	15/50 (NS)
		all lymphomas	17/50 (NS)	16/50 (NS)	17/50 (NS)
		lymphoma or leukemia	17/50 (NS)	16/50 (NS)	18/50 (NS)

[a] Source: NTP, 1982a

[b] p-Values next to the control incidences indicate the probability level for the Cochran-Armitage test; p-values next to dosed-group incidences indicate the probability level for the Fisher Exact Test.

[c] N indicates a negative trend, that is, the incidence for dosed groups is lower than for controls.

NS = Not significant; p-value >0.05

benzyl phthalate may cause leukemia in humans. IARC (1982) concluded that the NTP (1982a) studies were insufficient to assess the carcinogenic potential of n-butyl benzyl phthalate. U.S. EPA (1985a) is currently reviewing this issue.

5.1.2. Di(2-ethylhexyl) Phthalates. Di(2-ethylhexyl) phthalate was fed to groups of 50 male and 50 female F344 rats at levels of 0, 6000 or 12,000 ppm, and to groups of 50 male and 50 female B6C3F1 mice at levels of 0, 3000 or 6000 ppm for 103 weeks (NTP, 1982b; Kluwe et al., 1982b). Average doses calculated from data on food consumption and body weight were 322 and 674 mg/kg/day for low- and high-dose male rats, 394 and 774 mg/kg/day for low- and high-dose female rats, 672 and 1325 mg/kg/day for low- and high-dose male mice, and 799 and 1821 mg/kg/day for low- and high-dose female mice, respectively. Throughout the study, food consumption, body weight, mortality and clinical signs of toxicity were monitored. Animals surviving 103 weeks on test were maintained for an additional 1-2 weeks after treatment, then evaluated by necropsy and histopathology. Animals that died before 103 weeks were evaluated similarly.

There were no compound-related effects on survival. A number of compound-related effects were observed when treated animals were compared with controls. A moderate decrease in body weight was observed in di(2-ethylhexyl) phthalate-treated female mice, but was not accompanied by a reduction in food consumption. Body weight was also reduced moderately in low- and high-dose male and high-dose female rats, but food consumption was also slightly reduced. A significantly higher incidence (Fisher Exact test) of hepatocellular carcinoma was observed in high-dose female rats, middle- and high-dose female mice and high-dose male mice (Table 5-3). A significantly greater incidence (Fisher Exact test) of hepatocellular carcinoma or

TABLE 5-3

Liver Neoplasms in F344/N Rats and B6C3F1 Mice Fed Di(2-ethylhexyl) Phthalate in the Diet for 103 Weeks[a]

Species	Sex	Tumor Type	Incidence (p-value)[b]		
			Control	Low Dose[c]	High Dose[c]
Rat	M	hepatocellular carcinoma	1/50 (0.047)	1/49 (NS)	5/49 (NS)
		hepatocellular carcinoma or neoplastic nodule	3/50 (0.007)	6/49 (NS)	12/49 (0.01)
	F	hepatocellular carcinoma	0/50 (0.002)	2/49 (NS)	8/50 (0.003)
		hepatocellular carcinoma or neoplastic nodule	0/50 (<0.001)	6/49 (0.012)	13/50 (<0.001)
Mouse	M	hepatocellular carcinoma	9/50 (0.018)	14/48 (NS)	19/50 (0.022)
		hepatocellular carcinoma or adenoma	14/50 (0.002)	25/48 (0.013)	29/50 (0.002)
	F	hepatocellular carcinoma	0/50 (<0.001)	7/50 (0.006)	17/50 (<0.001)
		hepatocellular carcinoma or adenoma	1/50 (<0.001)	12/50 (0.001)	18/50 (<0.001)

TABLE 5-3 (cont.)

QUALITY OF EVIDENCE

Strengths of Study:	Lifetime study of both sexes of two species; adequate number of animals tested at MTD; relevant route of exposure; appropriate statistical analysis; comprehensive histological examination.
Overall adequacy:	Adequate

[a] Source: NTP, 1982b

[b] The p-value next to the control incidence indicates the probability level for the Cochran-Armitage Test; the p-value next to the dosed group incidence indicates the probability level for the Fisher Exact Test.

[c] Rats were given dietary concentrations of 6000 and 12,000 ppm; mice were given 3000 and 6000 ppm.

NS = Not significant; p-value >0.05

neoplastic nodules was observed in high-dose male rats, middle- and high-dose female rats and a significantly greater incidence of hepatocellular carcinoma or adenoma was observed in middle- and high-dose male and female mice (see Table 5-3). Significantly decreased incidences of interstitial cell tumors of the testes, pituitary carcinoma or adenoma and thyroid C-cell carcinoma or adenoma were also observed in high-dose male rats. Significant compound-related increases in seminiferous tubule degeneration (rats and mice) and hypertrophy of cells in the anterior pituitary (male rats) were also observed.

NTP (1982b), Kluwe et al. (1982b), U.S. EPA (1985a) and IARC (1982) concluded that these results provide sufficient evidence of di(2-ethylhexyl) phthalate-induced carcinogenicity in rats and mice. This conclusion, however, is disputed. Northrup et al. (1982) claim that the NTP (1982b) results are equivocal since the MTD was exceeded in some treatment groups, incidences of liver tumors varied within different control groups of the same species and sex, and treated animals may have been malnourished. Northrup et al. (1982) also claimed that the rodent data cannot be used to predict carcinogenic risk in humans because di(2-ethylhexyl) phthalate is metabolized differently in rats than in humans. In response, Kluwe et al. (1983) noted that MTD was not technically exceeded since there were no compound-related effects on survival, the incidence of liver tumors was increased in di(2-ethylhexyl) phthalate-treated animals regardless of the control data used and the differences in metabolism between rodents and humans would not affect the carcinogenic response in rodents. More recently, Turnbull and Rodricks (1985) concluded that using NTP (1982b) data to estimate di(2-ethylhexyl) phthalate-induced carcinogenic risk to humans will probably overestimate actual risk. This conclusion was based on the differences between rodents and primates in the metabolism of di(2-ethylhexyl) phthalate, a nonlinear relationship between the administered dose of di(2-ethylhexyl) phthalate to the dose of the "proximate carcinogenic species" in rodents, the fact that the "proximate carcinogenic species," which is hypothesized to induce cancer, is produced to a greater extent in rodents than in primates and that there are differences in target-site sensitivity between humans and rodents for liver tumors in general.

In conclusion, results of NTP bioassays indicate that di(2-ethylhexyl) phthalate is carcinogenic for B6C3F1 mice and F344 rats of both sexes but are only limited to assess the carcinogenic potential of n-butyl benzyl phthalate. The relevance of these studies to the carcinogenic potential of pthalate esters in humans is questionable. Pertinent data regarding the carcinogenicity of phthalates in humans could not be located in the available literature as cited in the Appendix. Adequate cancer bioassays have not been conducted for other pthalate esters.

5.2. MUTAGENICITY

Thomas and Thomas (1984) and Hopkins (1983) reviewed the mutagenicity and genotoxicity of di(2-ethylhexyl) phthalate, its metabolites and other phthalic acid esters. Di-2(ethylhexyl) phthalate and its metabolites, monoethylhexyl phthalate and 2-ethylhexanol, have been tested extensively in Ames assays with Salmonella typhimurium with and without metabolic activation. Negative results have been reported by Zeiger et al. (1982), Kirby et al. 1983, Kozumbo et al. (1982), Ruddick et al. (1981), Simmon et al., (1977), Warren et al. (1982), and Yoshikawa et al. (1983). Di(2-ethylhexyl) phthalate was also found not to cause reverse mutation in Escherichia coli with and without S9 (Tomita et al., 1982a; Yoshikawa et al., 1983). Kozumbo et al. (1982) and Rubin et al. (1979) reported that dimethyl and diethyl phthalates were mutagenic in strain TA100 of S. typhimurium but only in the absence of S9. Seed (1982) reported that dimethyl, diethyl (with and without S9) and di-n-butyl phthalates (without, but not with, S9), but not di(2-ethylhexyl), di-n-octyl, diisodecyl and diisobutyl phthalates, were found to cause mutation to 8-azaguanine resistance in bacterial suspension assays with S. typhimurium; the di(2-ethylhexyl) phthalate metabolite, 2-ethylhexanol, was found to be mutagenic without S9. Tomita et al. (1982a) reported that monoethylhexyl, but not di(2-ethylhexyl), phthalate yielded positive results in rec assays with Bacillus subtilis.

With two exceptions, in vitro genotoxicity assays have yielded negative results. Di-2(ethylhexyl) phthalate failed to cause an increase in chromosomal aberrations in human lymphocytes (Turner et al., 1974), in Chinese hamster fibroblasts (Abe and Sasaki, 1977; Ishidate and Odashima, 1977), and in CHO cells (Phillips et al., 1982). Di-2(ethylhexyl) phthalate did not cause aneuploidy in human fetal lung cells (Stenchever et al., 1976). Di(2-ethylhexyl) phthalate and its metabolites (monoethylhexyl and 2-ethylhexanol) failed to induce unscheduled DNA synthesis in primary rat hepatocytes (Hodgson et al., 1982). Monoethylhexyl phthalate was reported to cause an increase in chromosomal aberrations and SCE in Chinese hamster V79 embryonic cells (Tomita et al., 1982a) and CHO cells (Phillips et al., 1982).

Chromosomal aberrations were observed in embryonic cells in a study in which Syrian golden hamsters were treated orally with 3.75-15 g/kg di(2-ethylhexyl) phthalate on day 11 of gestation (Tomita et al., 1982a). Putman et al. (1983) failed to observe significant increases in clastogenic changes in bone marrow cells taken from male F344 rats treated by gavage with di(2-ethylhexyl) phthalate (0.5-5 g/kg/day) or monoethylhexyl phthalate

(0.01-0.14 g/kg/day) for 5 days. Positive results were observed in a dominant/lethal study on ICR mice, where di(2-ethylhexyl) phthalate was administered as a single intraperitoneal dose (2/3 LD_{50}) (Singh et al., 1974).

Agarwal et al. (1985b) evaluated the antifertility and mutagenic effects of DEHP in ICR mice. In the first phase of the study, eight male mice per group were given DEHP by s.c. injection at doses of 0.99, 1.97, 4.93 and 9.86 g/kg on days 1, 5 and 10 of the experiment. Sixteen control animals were given saline by s.c. injection. On day 21, each male was housed with a female for 7 days.

In phase two, five groups of 10 male mice each were injected with 0, 0.99, 1.93, 4.93 and 9.86 mg/kg DEHP on days 15 and 10 of the experiment. One untreated female mouse was housed with each male at each treatment interval. After the last dose, females were replaced at 5-day intervals for the first 21 days and at 7-day intervals through a total of 8 weeks from the start of the experiment.

The females were sacrificed 13 days from the middle of their respective periods of cohabitation. The uterine horns and ovaries were examined for total number of corpora lutea, implantations, early fetal deaths and viable fetuses. The difference between the number of corpora lutea and the number of implantations was calculated to reflect preimplantation loss. The data for all endpoints were evaluated in three time frames: the first 3 weeks of the study, the final 5 weeks and the totals for the 8 weeks.

Mutagenicity was evaluated utilizing two indices: preimplantation loss/implants per pregnancy and early fetal deaths/implants per pregnancy.

In the phase I study there was a reduction in the incidence of pregnancies. Although preimplantation loss appeared to be somewhat greater in the treated groups, none of these differences were significant ($p \leq 0.05$).

In contrast, early fetal death was significantly increased in all treated groups. The numbers of viable fetuses were significantly reduced in the lowest and highest dose groups only. Both of the mutagenicity indices were increased in all of the treated groups (statistics not reported).

In the phase II study, there was no effect of DEHP on the incidence of pregnancies. The number of implantations were reduced in the 1.93 and 9.86 g/kg groups in the day 2 to 21 interval, but not in the 4- to 8-week interval. Combining across weeks (1-8) there was a reduction in implantations for the high dose alone. Preimplantation loss was increased in all dose groups for the early study interval and for the total 8-week period. Early deaths were increased for all dose groups for all three time intervals. The number of viable fetuses was significantly decreased during the first study segment and for the total 8 weeks. The preimplantation loss mutagenicity index was significantly increased during the early study segment in the 0.99, 1.97 and 0.86 mg/kg groups and for the overall study (weeks 1-8) in the 1.97, 4.93 and 0.86 mg/kg dose groups. The early death index was significantly increased for all doses at all study segments.

In experiments with F344 rats, Albro et al. (1982) showed that radiolabeled di(2-ethylhexyl) phthalate and monoethylhexyl phthalate (but not ethylhexanol) associated strongly with DNA. Covalent binding, however, was not demonstrated.

5.3. TERATOGENICITY

A number of oral studies have shown that exposure to di(2-ethylhexyl), di-n-butyl and di-n-heptyl phthalates during gestation can have adverse effects upon the developing fetus. Whether the observed effects (reduced fetal weight, fetal mortality, gross external and skeletal malformations) represent a primary effect of the compound in question or whether they occur as a result of maternal toxicity has yet to be demonstrated unequivocally. Oral studies concerning di(2-ethylhexyl) phthalate are summarized in Table 5-4.

Di-2(ethylhexyl) phthalate-induced fetotoxic and teratogenic effects have been reported in rats and mice (Wolkowski-Tyl et al., 1984a,b; Bell et al., 1979; Bell, 1980; Shiota and Mima, 1985; Shiota and Nishimura, 1982; Shiota et al., 1980; Nakamura et al., 1979; Yagi et al., 1978, 1980; Tomita et al., 1982b; Onda et al., 1974; Nikonorow et al., 1973). Studies conducted by NTP (Wolkowski-Tyl et al., 1984a,b) indicate that mice are more sensitive to di(2-ethylhexyl) phthalate than rats. The studies that show effects at the lowest level of exposure and in the absence of maternal toxicity report a significantly increased incidence of percent of malformed fetuses/litter in CD-1 mice whose dams were fed 91 mg/kg/day throughout gestation (Wolkowski-Tyl et al., 1984b); significantly decreased fetal body weight in ddY-SlcXCBA mice whose dams were gavaged with 0.05 mℓ/kg (49 mg/kg) on day 7 of gestation (Tomita et al., 1982b); and the formation of renal cysts in the F_1 and F_2 generations of mice exposed orally (not specified) to 10 or 100 mg/kg/day for 3 generations (Onda et al., 1974); (no other details provided). The decreased fetal body weights observed by Tomita et al. (1982b) were not observed in ICR or CD-1 mice treated at somewhat higher (0.05% diet or ~65 mg/kg/day) or lower (44 mg/kg/day) doses throughout gestation (Wolkowski-Tyl et al., 1984b; Shiota et al., 1980; Shiota and Nishimura, 1982). The study conducted by Wolkowski-Tyl et al. (1984b) is thorough and well-reported, and provides a NOEL of 44 mg/kg/day and a LOAEL of 91 mg/kg/day for di(2-ethylhexyl) phthalate-promoted teratogenic effects.

TABLE 5-4

Summary of Oral Teratogenicity Studies with Di(2-ethylhexyl) Phthalate

Species/ Strain	Dose, Vehicle and Duration of Treatment	Endpoints Monitored	Maternal Response	Fetal Response	Reference
Rat/F344	0, 0.5, 1.0, 1.5 or 2% diet (0, 356.7, 666.4, 856.5 or 1054.8 mg/kg/day) on days 0-20 of gestation	standard NTP teratology study	dose-related decrease in bw, significant at ≥1%; significant dose-related increase in absolute and relative liver weight, significant at all doses; significant dose-related decrease in gravid uterine weight, significant at 2%	Dose-related increase in % resorptions/litter, % nonlive/litter (dead and resorbed), and number of affected fetuses/litter (nonlive and malformed), significant at 2%; dose-related decrease in bw, significant at all doses; significant dose-related increase in % malformed fetuses/litter but no statistically significant pairwise differences	Wolkowski-Tyl et al., 1984a
Rat/NR	2.5 or 5.0 mL/kg on days 7-13 of gestation (vehicle NR)	NR	NR	No teratogenic effects; 50% resorption of implants at 2.5 mL/kg; no other details	Nakayama, 1968
Rat/Sprague-Dawley	0, 0.5 or 1% diet on last 16 days of gestation and throughout lactation	sterologenesis in livers of pups 8 days after birth	NR	(Both doses) significant reduced sterologenesis; significant reduced body weight; significant increased related liver weight	Bell et al., 1979
Rat/Sprague-Dawley	0, 0.5 or 1% diet for 5-10 days after mating	sterologenesis in brain and liver of 18-day fetuses	NR	(Both doses) significant reduced sterologenesis in brain and liver	Bell et al., 1979
Rat/Sprague-Dawley	0, 0.5% diet on days 5-18 of gestation	sterologenesis in livers of fetuses and dams	reduced sterologenesis	Reduced sterologenesis (not statistically significant)	Bell, 1980
Rat/Wistar	0, 0.34 or 1.7 g/kg/day in olive oil for 3 months before mating or 0, 0.34 or 1.7 g/kg/day in olive oil on days 0-21 of gestation	day 21 of gestation: number live fetuses; number dead fetuses; number resorptions; fetal body weight, placental body weight, skeletal examination of fetuses; placental weight	NR	No effects when administered before gestation; significantly reduced fetal body weight when administered during gestation (high dose); significantly reduced placental weight (both doses); increased number of resorptions (high dose); no skeletal effects	Nikonorow et al., 1973
Mouse/CD-1	0, 0.025, 0.05, 0.1 or 0.15% diet (0, 44, 91, 191 or 292 mg/kg/day) on days 0-18 of gestation	standard NTP teratology study	Dose-related decrease in body weight, significant at 0.1 and 0.15%; dose-related increase in related liver weight, significant at 0.1 and 0.15%	dose-related increase in % resorptions/litter, dead/litter, nonlive/litter (dead nd resorbed), and affected fetuses/litter (dead and malformed), significant at 0.1 and 0.15%; significant decrease in fetal body weight at 0.15%; significant increases in % malformed fetuses/litter at 0.05, 0.1 and 0.15% (external, visceral and skeletal defects)	Wolkowski-Tyl et al., 1984b

TABLE 5-4 (cont.)

Species/ Strain	Dose, Vehicle and Duration of Treatment	Endpoints Monitored	Maternal Response	Fetal Response	Reference
Mouse/S/C-ICR	0, 250, 500, 1000 or 2000 mg/kg in olive oil on days 7-9 of gestation	day 18 of gestation: number of abortions, maternal mortality, resorptions, implants, dead fetuses, fetal body weight, gross external anomalies	3/11 aborted and 1/11 died at 2000 mg/kg; abortions and mortality were not observed at any other level	(1000 and 2000 mg/kg) significant increases in % resorptions and dead fetuses, and % malformed fetuses (exencephaly/anencephaly; tail anomalies); decreased fetal body weight	Shiota and Mima, 1985
Mouse/ICR	0, 0.05, 0.1, 0.2, 0.4 or 1% diet on days 0-18 of gestation	day 18 of gestation: maternal body weight; number resorptions; number implants; number dead fetuses; fetal body weight; gross external, skeletal and visceral anomalies	significant decreased body weight at 0.2, 0.4 and 1%	100% early resorption (all implants) at 0.4 and 1%; significant increased % resorptions at 0.1 and 0.2%; significant increased % fetuses with gross external malformations (neural tube defects) at 0.2, 0.4 and 1%	Shiota and Nishimura, 1982; Shiota et al., 1980
Mouse/random strain ddY-Slc x CBA	0, 0.05, 0.1 or 1 mℓ/kg on day 7 of gestation (no vehicle)	day 18 of gestation: maternal body weight, number implants, early and late resorptions, number live, gross external and skeletal malformations	(1 mℓ/kg) slight decrease in body weight on day 14 of gestation	(1 mℓ/kg) increased incidence of gross and skeletal anomalies (elongated and fused ribs, absence of tail and leg bones) (0.1 and 1 mℓ/kg) significant increased fetal mortality	Nakamura et al., 1979
Mouse/ddY-Slc x CBA	various doses on day 6, 7, 8, 9 or 10 of gestation (gestation day 6) 2.5 mℓ/kg (7) 1, 2.5 or 5 mℓ/kg (8) 7.5 or 10 mℓ/kg (9) 7.5, 10 or 30 mℓ/kg (10) 10 or 30 mℓ/kg (no vehicle)	day 18 of gestation: maternal body weight, number implants, number early and late resorptions, number live fetuses with gross external or skeletal anomalies	decreased body weight at all doses given on days 6, 7 or 8 of gestation	Significant reduced fetal body weight at all doses on all days; increased fetal mortality and resorptions at all doses on days 7 and 8 of gestation; dose-related increase in incidences of gross external and skeletal anomalies on days 7 and 8 of gestation (all doses); some external anomalies but no skeletal anomalies on days 9 or 10 of gestation (10 and 30 mℓ/kg on day 9, 30 mℓ/kg on day 10); no resorptions, dead fetuses, or gross or skeletal anomalies were observed in controls	Yagi et al., 1978, 1980; Tomita et al., 1982a
Mouse/ddy-Slc x CBA	0, 0.05, 0.1 or 1 mℓ/kg on day 7 of gestation (no vehicle)	same as above	decreased body weight at 1 mℓ/kg	Significant reduced fetal body weight at all doses; significant increase in incidences of gross and skeletal anomalies at 1%; decreased % live fetuses at 0.1 and 1%	Tomita et al., 1982b
Mouse/ddy-JCL and ICR	0, 10 or 100 mg/kg/day for 3 generations (vehicle NR)	NR	NR	Formation of renal cysts in F_1 and F_2 (both doses)	Onda et al., 1974

NR - Not reported

Studies concerning phthalic acid esters other than di(2-ethylhexyl) phthalate are summarized in Table 5-5. In separate reports of the same study, Booth et al. (1983) and Plasterer et al. (1985) reported that dimethyl phthalate had no effects on reproduction in CD-1 mice. Groups of 50 female mice were gavaged with 0 or the MTD of dimethyl phthalate (3500 mg/kg in corn oil) on days 7-15 of gestation, and allowed to deliver naturally. There were no significant effects on survival, body weight, birth weight of pups, or average number live/litter, average number dead/litter, or average weight of pups on days 1 and 3 postpartum. The pups were not examined for malformations.

Shiota et al. (1980) and Shiota and Nishimura (1982) reported teratogenic and fetotoxic effects in mice caused by di-n-butyl phthalate, but only at a dietary concentration (1%) that also produced a significant depression of maternal weight gain. No effects on the fetuses or dams were observed in mice fed ≤0.4% di-n-butyl phthalate throughout gestation. In a 3-generation study, Onda et al. (1974) observed renal cyst formation in the F_1 and F_2 generations of mice exposed orally (not specified) to 10 or 100 mg di-n-butyl phthalate/kg/day; however, no other details were given. An increased number of resorptions and significantly reduced fetal body weights were observed in rats gavaged with 600 mg di-n-butyl phthalate/kg/day throughout gestation (Nikonorow et al., 1973); reduced placental weights were observed in mice gavaged with 120 or 600 mg di-n-butyl phthalate/kg/day. Unfortunately, this study did not randomly select test animals and did not examine gross or visceral malformations.

It is difficult to define a dose-response relationship for di-n-heptyl phthalate. The only study, Nakashima et al. (1977), is poorly reported.

TABLE 5-5

Summary of Oral Teratogenicity Studies for Phthalic Acid Esters Other Than Di(2-ethylhexyl) Phthalate

Species/ Strain	Dose, Vehicle and Duration of Treatment	Endpoints Monitored	Maternal Response	Fetal Response	Reference
		DIMETHYL PHTHALATE			
Mouse/CD-1	0 or 3500 mg/kg/day on days 7-15 of gestation	dams were allowed to deliver; dams observed for survival and body weight, pups observed for birth weight, number of live/litter, dead/litter, average weight on day 1 or 3 postpartum	no effect	No effects; pups were not examined for malformations	Booth et al., 1983; Plasterer et al., 1985
		DI-n-BUTYL PHTHALATE			
Rat/Wistar	0, 0.12 or 0.60 g/kg/day in olive oil for 3 months prior to mating or 0, 0.12 or 0.60 g/kg/day in olive oil on days 0-21 of gestation	day 21 of gestation: number live fetuses; number resorptions; fetal body weight, placental body weight; skeletal examination of fetuses; placental weight	NR	No effects when DBP was administered prior to gestation; significantly reduced fetal body weight when administered during gestation (0.6 g/kg/day); increased number resorptions (0.6 g/kg/day); significant reduced placental weight (both doses); no skeletal effects	Nikonorow et al., 1973
Mouse/ICR	0, 0.05, 0.1, 0.2, 0.4 or 1% diet on days 0-18 of gestation (0, 80, 180, 370, 660 or 2100 mg/kg/day)	day 18 of gestation: maternal body weight, number resorptions, number implants, number dead fetuses, fetal body weight, gross external, skeletal and visceral anomalies	significant decreased body weight at 1%	Significant increase in number of resorptions and dead fetuses at 1%; significant increase in incidence of gross external malformations at 1%; significant decreased number of ossified coccygia at all levels of treatment	Shiota et al., 1980; Shiota and Nishimura, 1982
Mouse/ddY/JCL and ICR	0, 10 or 100 mg/kg/day for 3 generations (vehicle NR)	NR	NR	Formation of renal cysts in F_1 and F_2 (no other details)	Onda et al., 1974
		DI-n-HEPTYL PHTHALATE			
Mouse/ICR:JCL	administered various doses on either day 7, 8, 9, 10 or 11 of gestation (day 7) 0.94, 1.88 or 3.75 mℓ/kg (8) 1.50, 2.50 or 7.50 mℓ/kg (10) 7.50, 11.3 mℓ/kg (11) 7.50, 11.3 mℓ/kg	embryo/fetotoxicity (NOS) gross external and skeletal anomalies	NR	Dose-response relationships not clearly presented; high incidence of gross external anomalies on days 7 and 8 of gestation at 2.5 and 7.5 mℓ/kg; embryo/fetotoxicity highest on days 7 and 8; 100% resorptions at 7.5 mℓ/kg (no other information); high incidence of skeletal anomalies on day 8, 100% with fused ribs at 2.5 mℓ/kg (no other information); gross anomalies included open eyelid, cleft palate and oligodactylia on day 9, exencephaly on day 8, and tail anomaly, oligodactylia and hematoma on days 10 and 11	Nakashima et al., 1977

NOS = Not otherwise specified; NR = not reported

Fetotoxic and teratogenic effects were observed, but the study seemed to focus on which days of gestation the mice were more likely to be sensitive to exposure, and there was no consistent effort to report which effects occurred at each particular dose. Furthermore, maternal effects were not reported.

A recent study indicates that phthalic acid esters may cause adverse effects when transported to the developing organism by milk. Parmar et al. (1985) observed a decrease in weight gain and changes in enzyme levels indicative of liver damage in 21-day-old rat pups whose dams were gavaged with 2000 mg di(2-ethylhexyl) phthalate/kg throughout lactation.

A number of intraperitoneal studies have been conducted with phthalic acid esters on rats (Singh et al., 1972). Given the route-dependent differences in absorption, distribution and excretion of phthalic acid esters, the relevance of intraperitoneal studies to oral risk assessment is uncertain. Singh et al. (1972) reported that parenterally administered dimethyl phthalate (0.38-1.125 mℓ/kg), diethyl phthalate (0.506-1.686 mℓ/kg), di-n-octyl phthalate (5, 10 mℓ/kg), di(2-ethylhexyl) phthalate (10 mℓ/kg) and di-n-butyl phthalate (0.3-1.017 mℓ/kg) caused fetotoxic or teratogenic effects when administered to rats on days 5, 10 and 15 of gestation.

5.4. OTHER REPRODUCTIVE EFFECTS

NTP recently conducted reproduction and fertility assessments on CD-1 mice for diethyl phthalate (Reel et al., 1984) and di-n-octyl phthalate (Gulati et al., 1985), using a new protocol, "fertility assessment by continuous breeding." The protocol consists of four tasks: 1) a range-finding study to determine maximum tolerated dose; 2) a continuous breeding study entailing exposure during 7 days before mating, followed by 98 days of cohabitation and 21 days of segregation; 3) a crossover breeding study to determine the affected sex; and 4) a reproductive performance assessment of control and high-dose litters from Task 2. Task 3 is performed only if adverse effects are detected in Task 2. If no adverse effects are detected in Task 2, then Task 4 is performed.

Based on the range-finding studies, dietary concentrations of 0, 0.25, 1.25 and 2.5% diethyl phthalate and 0, 1.25, 2.5 and 5% di-n-octyl phthalate were chosen for Task 2. No adverse compound-related effects (number of pairs able to produce at least one litter, number of litters/pair, proportion of pups born alive, sex of pups born alive, live pup weight) were observed for either diethyl phthalate or di-n-octyl phthalate; Task 4 was therefore performed for both compounds. Endpoints monitored for Task 4 include body weight at weaning and at 74 days of age, mating behavior, reproductive performance as measured in Task 2 (beginning at 74 days of age), sperm assessment and selected organ weights. F_1 male and female pups born to dams fed 2.5% diethyl phthalate had significantly lower body weights than controls at weaning and at 74 days of age. The diethyl phthalate-exposed F_1 had significantly fewer live pups per litter than did controls. Males had significantly reduced sperm concentrations and significantly increased prostate weights in comparison with controls. Both males and females exposed to diethyl phthalate had significantly increased liver weights; females also had significantly increased pituitary weights. In contrast, there were no significant, adverse compound-related effects on fertility, reproduction or organ weights in F_1 mice exposed to 5% di-n-octyl phthalate.

The fertility of Sherman rats was not affected by dietary exposure to di(2-ethylhexyl) phthalate (up to 0.4%). Significantly increased relative kidney and liver weights, however, were observed in F_1 males and females (Carpenter et al., 1953) (Section 5.5.1.).

The testicular effects of phthalic acid esters have been studied extensively in rats. Orally administered di(2-ethylhexyl) phthalate, di-n-butyl phthalate, n-butyl benzyl phthalate, di-n-pentyl phthalate, di-isobutyl phthalate, and di-n-hexyl phthalate cause testicular atrophy characterized in general by reduced testicular weight, histological evidence of degeneration, reduced testicular zinc concentration and either an increase or decrease in testicular testosterone concentration (Gray et al., 1977, 1982; Gangolli, 1982; Oishi and Hiraga, 1980a, 1983; Gray and Butterworth, 1980; Mangham et al., 1981; Oishi, 1985; Agarwal et al., 1985; Cater et al., 1976, 1977; NTP, 1982b; Kluwe et al., 1982b; Foster et al., 1980). These studies are summarized in Table 5-6. Cater et al. (1977) demonstrated that co-administration of zinc could counteract the degenerative effects of di-n-butyl phthalate, while Oishi and Hiraga (1983) demonstrated that co-administration of zinc had no effect on di(2-ethylhexyl) phthalate-promoted atrophy. Furthermore, Gray and Butterworth (1980) demonstrated that when rats were removed from di(2-ethylhexyl) phthalate exposure, testicular weight and morphology were restored within 12-20 weeks of exposure; Oishi (1985) observed only slight recovery after 45 days. Equimolar concentrations (compare with effective phthalic acid esters) of dimethyl phthalate, diethyl phthalate, dipropyl phthalate, di-n-heptyl phthalate and di-n-octyl phthalate did not cause testicular atrophy in rats when administered orally for 4-10 days (Gray and Butterworth, 1980; Foster et al., 1980).

Sjöberg et al. (1985) investigated the kinetics of orally administered DEHP in 25-, 40- and 60-day-old male Sprague-Dawley rats in an attempt to elucidate the greater testicular sensitivity to this compound in young animals. For the toxicity study, groups of 7-8 rats/group from each of the three age designations were treated by gavage with either 1 g DEHP/kg in

TABLE 5-6

Orally Administered Phthalate Esters Causing Testicular Atrophy in Rats

Compound	Vehicle	Effective Dose(s)	Duration	Reference
DEHP	diet	1.0, 2.0% (750, 1500 mg/kg/day)	90 days	Gangolli, 1982*
	diet	12,000 ppm (674 mg/kg/day)	104 weeks	NTP, 1982b; Kluwe et al., 1982b
	diet	1.0, 2.0%	17 weeks	Gray et al., 1977*
	diet	2%	7 days	Oishi and Hiraga, 1980a
	diet	2% (1200 mg/kg/day)	10 days	Gray and Butterworth, 1980
	diet	1.5 or 3%	90 days	Shaffer et al., 1945
	corn oil	2800 mg/kg/day	10 days	Gray and Butterworth, 1980
	corn oil	2800 mg/kg/day	9 days	Gray et al., 1982
	corn oil	2500 mg/kg/day	21 days	Mangham et al., 1981
	none; gavage	2000 mg/kg/day	10 days	Oishi and Hiraga, 1983
	none; gavage	2000 mg/kg/day	14 days	Oishi, 1985
BBP	diet	2.5 or 5.0%	14 days	Agarwal et al., 1985
DBP	corn oil	2000 mg/kg/day	4-9 days	Cater et al., 1976
	corn oil	equimolar to 2800 mg DEHP/kg	10 days	Gray and Butterworth, 1980
	corn oil	2000 mg/kg	9 days	Gray et al., 1982
	corn oil	500, 1000, 2000 mg/kg/day	6 days	Cater et al., 1977
DPeP	Corn oil	2200 mg/kg/day	4 days	Gray et al., 1982
	corn oil	2100 mg/kg/day	4 days	Foster et al., 1980
	corn oil	equimolar to 2800 mg DEHP/kg/day	10 days	Gray and Butterworth, 1980
DIBP	diet	2%	7 days	Oishi and Hiraga, 1980a
DHP	corn oil	equimolar to 2800 mg DEHP/kg/day	10 days	Gray and Butterworth, 1980
	corn oil	2400 mg/kg/day	4 days	Foster et al., 1980

*These are probably the same study

corn oil or with corn oil alone daily for 14 days. Body weights and the following organ weights were recorded: liver, testes, ventral prostate seminal vesicles. In addition, testes were fixed, sectioned and evaluated using light microscopy.

For the kinetic study, groups of 9-10 rats from each of the three age designations were utilized. DEHP at a dose of 1 g/kg was administered as a single gavage dose. Blood samples were drawn from a jugular cannula at 1, 3, 5, 7, 9, 12, 15, 24 and 30 hours postdosing (0.25 mℓ/sample). DEHP and MEHP analysis was conducted on hexane extracts by gas chromatography.

For the excretion studies, two groups of six rats each were utilized. One group consisted of 25-day-old animals and the other of 60-day-old animals. Each animal received 1 g ^{14}C-DEHP/kg in corn oil by gavage. Urine was collected each day for 3 days. Excretion was quantified by scintillation counting. In addition, aliquots of urine were extracted, evaporated, dissolved in diethyl ether and streaked on thin layer plates of silica gel. Standards of DEHP and MEHP were utilized. Radioactive zones were located utilizing a radio scanner.

For the *in vitro* metabolism evaluations, four groups of six rats each were utilized. Groups consisted of two groups of 25-day -old animals, one pretreated with phenobarbital and the other not pretreated. The same procedure was followed with the 60-day-old animals. DEHP was given by gavage in corn oil at a dose of 1 g/kg/day for 14 days. Phenobarbital was given by i.p. injection of three daily doses of 100 mg/kg. Liver microsomal preparations were utilized to evaluate the rate of conversion of MEHP to its hydroxylated product, mono-(2-ethyl-5-hydroxyhexyl)phthalate.

Protein binding of MEHP to blood plasma from 25-, 40- and 60-day-old rats was also evaluated. This was accomplished using ^{14}C-MEHP and an equilibrium dialysis technique.

The 25-day-old rats were the only age group exhibiting significantly reduced testicular weights. Liver weights were increased in all treated groups in the toxicity study. The testes of the 25-day-old animals showed severely affected seminiferous tubules. The cell type most affected was the primary spermatocyte. Some spermatogonial involvement was also seen. No abnormalities were seen in animals from the other age groups.

No age-related differences were seen in maximum MEHP plasma concentration or MEHP plasma elimination half-lives. The mean area under the MEHP plasma concentration curve was significantly greater in 25-day-old rats than in 40- or 60-day-old rats. Cumulative excretion of ^{14}C-DEHP was 44 and 26% of the administered dose for 25- and 60-day-old rats, respectively. Significant differences were not seen in conversion of MEHP to mono-(2-ethyl-5-hydroxyhexyl)phthalate using liver microsomes from 25- and 60-day-old rats. Significant differences among the age groups in binding of MEHP to plasma proteins were not seen.

The authors concluded that their data suggested that the increased susceptibility of young rats to the testicular effects of DEHP may in part be explained by greater absorption of DEHP from the gastrointestinal tract of the young animals based on he larger amount of excreted radioactivity and the increased area under the plasma MEHP concentration time curve in the young animals. The possibility of differential tissue sensitivity was also suggested.

Species differences in phthalic acid ester-promoted testicular atrophy have also been observed. Gray et al. (1982) failed to observe testicular atrophy in hamsters gavaged with di-n-butyl, di(2-ethylhexyl) and di-n-pentyl phthalates at equimolar doses equivalent to those that caused atrophy in rats. In the same study, mice gavaged with equimolar doses of di-n-butyl, di(2-ethylhexyl) and di-n-pentyl phthalates had only slight focal atrophy (Gray et al., 1982). B6C3F1 mice fed 6000 ppm (1325 mg/kg/day) di(2-ethylhexyl) phthalate in the diet for 103 weeks had a slight but significantly higher incidence of seminiferous tubule atrophy than did controls (NTP, 1982b; Kluwe et al., 1982b).

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Chronic or subchronic oral studies have been conducted with di(2-ethylhexyl), di-n-butyl, dimethyl, diisononyl, n-butyl benzyl and di-n-octyl phthalates. The liver, kidney and testes appear to be the organs affected most by phthalic acid esters.

5.5.1. Di-2(ethylhexyl) Phthalates. Oral studies with di(2-ethylhexyl) phthalate have been conducted on rats (Carpenter et al., 1953; Harris et al., 1955; Nikonorow et al., 1973; Gray et al., 1977; Popp et al., 1985; Ganning et al., 1985; Nagasaki et al., 1974; Maslenko, 1968; NTP, 1982b; Kluwe et al., 1982b; Shaffer et al., 1945), mice (NTP, 1982a; Ganning et al., 1985; Nagasaki et al., 1974; Ota et al., 1974), ferrets (Lake et al., 1976, 1977a), guinea pigs (Carpenter et al., 1953), and dogs (Carpenter et al., 1953, Harris et al., 1955). These studies are summarized in Table 5-7. The studies that show adverse effects at the lowest levels of exposure are those of Carpenter et al. (1953), Gray et al. (1977) and Nagasaki et al. (1974).

Carpenter et al. (1953) fed di(2-ethylhexyl) phthalate to rats, guinea pigs and dogs. Groups of Sherman rats (32/sex/group) were fed 0, 0.04, 0.13 or 0.4% di(2-ethylhexyl) phthalate in the diet (0, 20, 60 or 200 mg/kg/day doses provided by the investigators) for 2 years, and were allowed to breed within the first year. After 1 year, groups of eight males and eight

TABLE 5-7

Oral Toxicity Summary for Di(2-ethylhexyl) Phthalate

Species/Strain	Number and Sex	Dose, Vehicle and Duration of Treatment	Endpoints Monitored	Effects	Reference
Rat/Sherman	2 generations: P_1 = 32M and 32F/group (reduced to 8M and 8F/group after 1 year); F_1 = 32M and 32F/group	P_1: 0, 0.04, 0.13 or 0.4% diet (0, 20, 60, or 200 mg/kg/day) for 2 years; (F_1) 0, 0.4% diet (0, 190 mg/kg/day) for 1 year	body weight, mortality, food consumption, hematology, fertility, liver and kidney weights, histopathology (major organs)	(0.4%): significantly increased relative liver and kidney weights in P_1 males (1 year only) and F_1 males and females; no histopathological changes	Carpenter et al., 1953
Rat/F344	50M and 50F/ group	0, 6000, 12,000 ppm diet (0, 322, 674 mg/kg/day for males; 0, 394, 774 mg/kg/ day for females) for 105 weeks	body weight, mortality, food consumption, clinical signs of toxicity, gross and microscopic pathology	Moderate reductions in body weight in low- and high-dose males and in high-dose females; slight reductions in food consumption (all treated rats); increased incidence of hypertrophy of cells in the anterior pituitary (males only; 1/46, 0/43 and 22/49 for 0, low- and high-dose rats, respectively); seminiferous tubule degeneration (1/49, 2/44, 43/48 for 0, low- and high-dose rats, respectively	NTP, 1982b; Kluwe et al., 1982b
Rat/NR	NR/NR	0, 0.375, 0.75, 1.5 or 3% (0, 0.2, 0.4, 0.9, 1.9 g/ rat) for 90 days	growth, mortality, hematology, pathology (extent not reported)	(0.75-3%) slight decrease in growth (1.5, 3%) tubular atrophy and degeneration in testes	Shaffer et al., 1945
Rat/Wistar	43M and 43F/ group	0, 0.1, 0.5% diet for up to 24 months (interim kills at 3, 6, 12 months)	mortality, body weight, food consumption, organ weights, histopathology	Reduced body weight and food consumption in rats fed 0.5% DEHP; significant increases in absolute and relative liver and kidney weights in rats fed 5% DEHP (3 and 6 months; but not at 12 or 24 months)	Harris et al., 1955
Rat/Wistar	10M and 10F/ group 20M and 20F	0.34 or 3.40 g/kg/day for 3 months (gavage: vehicle-olive oil) 0 g/kg/day for 3 months (olive oil)	behavior; body weight; hematology; serum proteins; gross and microscopic examination of kidneys, liver and spleen	Increased mortality in high-dose group (75%); statistically significant increase in relative liver weight in low dose group (changes in high dose group NR)	Nikonorow et al., 1973
Rat/Wistar	20M and 20F/ group	0, 0.35% diet for 12 months	behavior; body weight; food consumption; hematology; serum proteins; gross and microscopic examination of liver, kidneys and spleen	Increased mortality (30% vs. 10%, controls); significantly decreased body weight; significantly increased relative liver weight; no histological changes	Nikonorow et al., 1973

TABLE 5-7 (cont.)

Species/Strain	Number and Sex	Dose, Vehicle and Duration of Treatment	Endpoints Monitored	Effects	Reference
Rat/Sprague-Dawley derived-CD	15M and 15F/group	0, 0.2, 1.0 or 2.0% diet (0, 150, 750, 1500 mg/kg/day) for 17 weeks	body weight, food consumption, clinical signs of toxicity, serum biochemistry, hematology, urinalysis, gross and microscopic pathology (major organs)	Reduced body weight gain and food consumption (1, 2%); significantly reduced packed cell volume (1, 2%); significantly reduced hemoglobin concentrations (1, 2%; males only); significantly increased relative and absolute liver weight (0.2, 1, 2%); dose-related increase in incidence of testicular damage (significant at 1, 2%) and castration cells in pituitary; significantly reduced relative and absolute testes weight (1, 2%)	Gray et al., 1977; Gangolli, 1982
Rat/CF-344/Cr/BR	10F/group	1.2% diet for 3 or 6 months	preneoplastic foci in liver	None	Popp et al., 1985
Rat/NR	NR/male	0.02, 0.2, 2% diet for -2 years	induction of hepatic and mitochondrial peroxisomes	Dose-related induction of palmitoyl CO-A dehydrogenase, carnitine acetyltransferase; induction of cytochrome P-450 (significant at 2% only)	Ganning et al., 1985
Rat/NR	NR/NR	500, 1000 ppm diet for 48 weeks	NR	Interstitial nephritis (more severe at 1000 ppm than at 500 ppm); increased SGPT; decreased blood glucose (500, 1000 ppm)	Nagasaki et al., 1974
Rat/NR	NR/NR	0.5 mg/kg/day (vehicle not reported) for 6 months	NR	None; recommend 2.5 mg/ℓ H_2O based on odor and taste	Maslenko, 1968
Mouse/B6C3F1	50M and 50F/group	0, 3000, 6000 ppm diet (0, 672, 1325 mg/kg/day, males; 0, 799, 1821 mg/kg/day, females) for 103 weeks	body weight, mortality, food consumption, clinical signs of toxicity gross and microscopic pathology	Moderately decreased body weight gain in low- and high-dose females; no effects on food consumption; increased incidence of seminiferous tubule degeneration (1/49, 2/48, 7/49 for 0, low and high dose, respectively)	NTP, 1982b; Kluwe et al., 1982b
Mouse/NR	NR/NR	500, 1000 ppm diet for 48 weeks	NR	No changes in SGPT or blood glucose	Nagasaki et al., 1974
Mouse	NR/NR	0.5, 5 g/kg/day diet for 1-3 months	NR	Degenerative changes in kidneys and liver	Ota et al., 1974

TABLE 5-7 (cont.)

Species/Strain	Number and Sex	Dose, Vehicle and Duration of Treatment	Endpoints Monitored	Effects	Reference
Ferret/albino	6-7/group (sex NR)	0, 1% diet for 14 months	biochemistry and ultrastructure of the liver	Marked enlargement of liver; significantly decreased activities of succenate dehydrogenase, aniline 4-hydroxylase, and microsomal glucose 6-phosphatase; decreased AP activity in centrilobular region; increased AP in midzonal region; increased smooth endoplasmic reticulum and numbers of lysosomes and autophagic vacuoles	Lake et al., 1977a
Ferret/albino (1150-1850 g)	6-7 males/ group	0, 1% (average = 1200 mg/ kg/day) diet for 14 months	enzyme activities, DNA content, and protein in liver homogenate and microsomal fractions; lipid peroxidation in microsomal fractions; microscopic (light and EM) examination of liver tissue; liver histochemistry; microscopic examination of major tissues; body weight	Significantly reduced body weight; significantly increased absolute liver weight; morphological and biochemical changes in liver; testicular damage	Lake et al., 1976
Guinea pigs/ hybrid, NOS	24M and 23F	0.13% diet for 1 year (64 mg/kg/day)	body weight, mortality, food consumption, hematology, liver and kidney weights, histopathology (major organs)	Significantly increased relative liver weight in females fed both doses; no other effects	Carpenter et al., 1953
	23M and 23F	0.04% diet for 1 year (19 mg/kg/day)			
	24M and 22F	0% diet for 1 year			
Dog/Cocker Spaniel; Wire-Haired Terrier	4/group, "randomly separated by breed and sex"	gelatin capsules; 0.03 mℓ/kg 5 times/week for 19 doses, then 0.06 mℓ/kg/day for 240 doses TWA = 54.7 mg/kg/day; controls given gelatin capsules only	body weight, liver and kidney weight, sulfobromophthalein test, plasma prothrombin time, plasma cholinesterase, gross and microscopic pathology (major organs)	None	Carpenter et al., 1953
Dog/mongrel	1 (sex NR)	0.06 mℓ/kg/day for 77 doses then 0.09 mℓ/kg/day for 169 doses (gavage with gelatin capsules) TWA = 79.3 mg/kg/day	same as above	Fatty vacuolation and congestion in liver; cloudy swelling and congestion in kidney	Carpenter et al., 1953
Dog/NR	1 (sex NR) no concurrent control	5 g/kg/day (gavage) for 14 weeks	body weight, hematology, gross and microscopic pathology (major organs)	chronic cholecystitis; some hemosiderosis of spleen	Harris et al., 1955
	1F; no concurrent control	0.1 g/kg diet for 14 weeks	body weight, hematology, gross and microscopic pathology	None	Harris et al., 1955

NR = Not reported; NOS = not otherwise specified females were continued on test for 1 year more. Groups of 32 male and 32 female progeny were chosen from the control and high-dose groups and placed on the appropriate control or high-dose diet for 1 year. Hybrid guinea pigs (~22-24/sex/group) were fed either 0, 0.04 or 0.13% di(2-ethylhexyl) phthalate in the diet (0, 19 or 64 mg/kg/day) for 1 year. Groups of four dogs (wire-haired terrier and cocker spaniel, "randomly separated by breed and sex") were kept as controls or fed gelatin capsules equivalent to a TWA of 54.7 mg/kg/day for a total of 259 daily doses (0.03 mℓ/kg 5 times/week for a total of 19 doses, then 0.06 mℓ/kg/day for 240 doses). One mongrel dog (sex not specified) was given gelatin capsules equivalent to a TWA of 79.3 mg/kg/day for a total of 246 daily doses (0.06 mℓ/kg for 77 doses, then 0.09 mℓ/kg for 169 doses). Body weight, mortality, food consumption, fertility, hematology, liver weights, kidney weights and histopathology (major organs) were monitored for the parental rats. All endpoints but fertility were assayed for the F_1 rats, guinea pigs and dogs. In addition, measurements of plasma prothrombin time and plasma cholinesterase, and the sulfobromophthalin test for liver function, were performed for dogs. Parental male rats and F_1 males and females fed 0.4% di(2-ethylhexyl) phthalate (200 mg/kg/day) had significantly increased liver and kidney weights, but no histopathological changes. No other compound-related effects were observed in rats. Significantly increased relative liver weight without accompanying histological change was observed in female guinea pigs fed 0.04 or 0.13% di(2-ethylhexyl) phthalate (19 or 64 mg/kg/day, respectively). Fatty vacuolation and congestion in the liver, and cloudy swelling and congestion in the kidneys were observed in the dog given a TWA dose equivalent to 79.3 mg di(2-ethylhexyl) phthalate/kg/day. No other effects were observed in dogs.

Gray et al. (1977) fed either 0, 0.2, 1.0 or 2.0% di(2-ethylhexyl) phthalate to groups of 15 male and 15 female Sprague-Dawley derived CD rats for 17 weeks. Dietary concentrations were equivalent to 0, 150, 750 and 1500 mg/kg/day as reported in a subsequent review (Gangolli, 1982). Body weight, food consumption, clinical signs of toxicity, serum biochemistry, urinalysis and hematology were monitored (Gray et al., 1977). Gross and microscopic pathology were performed on all animals at the end of the study. Effects were observed at all levels of exposure to di(2-ethylhexyl) phthalate. Significantly increased absolute and relative liver weights were observed in all di(2-ethylhexyl) phthalate-exposed groups. Food consumption and growth were reduced in rats fed either 1 or 2% di(2-ethylhexyl) phthalate. In comparison with controls, significantly reduced testicular weights, significantly increased testicular damage (dose-related) and a significant decrease in hemoglobin concentration were observed in male rats fed either 1 or 2% di(2-ethylhexyl) phthalate. Both males and females fed either 1 or 2% di(2-ethylhexyl) phthalate had a significantly reduced packed cell volume in comparison with controls. Nagasaki et al. (1974) reported that interstitial nephritis, increased SGPT and decreased blood glucose were observed in rats fed either 500 or 1000 ppm di(2-ethylhexyl) phthalate in the diet for 48 weeks. The dietary levels are equivalent to 25 or 50 mg/kg/day, respectively, assuming that a rat consumes a daily amount of food equal to 5% of its body weight. No other details were available.

5.5.2. **Diethyl Phthalate.** Toxicity studies of diethyl phthalate are summarized in Table 5-8. U.S. EPA (1980a) summarized a study by Food Research Laboratories (1955) in which groups of 30 rats (strain and sex not reported) were fed diethyl phthalate at concentrations of 0.5, 2.5 or 5.0% for 104 weeks. The dietary levels are equivalent to 250, 1250 or 2500 mg/kg/day, assuming a daily food consumption equal to 5% of the body weight.

TABLE 5-8

Oral Toxicity Summary for Diethyl Phthalate

Species/ Strain	Number and Sex	Dose, Vehicle and Duration of Treatment	Endpoints Monitored	Effects	Reference
Rat/NR	30/group (sex NR)	0.5, 2.5 or 5% diet for 104 weeks	NR	Small but significant reduction in body weight gain for rats fed 5% DEP; food consumption was not affected	Food Research Laboratories, 1955
Rat/CD	15 M and 15F/group	0, 0.2, 1.0 or 5% diet for 16 weeks	body weight, food consumption, water intake, hematology, urinalysis, serum biochemistries, gross and microscopic pathology	Significantly reduced body weight (males and females, 5%; females, 1%)	Brown et al., 1978
Dog/NR	3 (sex NR)	0.5% diet for 1 year	NR	None	Food Research Laboratories, 1955
	1 (sex NR)	1.5% diet for 1 year			
	1 (sex NR)	2.0% diet for 1 year			
	3 (sex NR)	2.5% diet for 1 year			

NR = Not reported

The only effect observed was a small but significant reduction in growth rate among rats fed 5% diethyl phthalate. Food consumption was not affected. U.S. EPA (1980a) did not report which endpoints were monitored in the study.

Food Research Laboratories (1955) also fed diethyl phthalate to dogs at concentrations of 0.5% (three dogs), 1.5% (one dog), 2.0% (one dog) and 2.5% (three dogs) for 1 year. Food consumption varied throughout the study; average doses as provided in the study were 114, 343, 500 and 629 mg/kg/day. No effects were observed at any level of exposure. Again, the endpoints which were monitored in the study were not reported.

Brown et al. (1978) fed groups of 15 male and 15 female CD rats either 0, 0.2, 1.0 or 5.0% di(2-ethylhexyl) phthalate (0, 150, 770 or 3160 mg/kg/day, males; 0, 150, 750 or 3710 mg/kg/day, females) in the diet for 16 weeks. Variables that were monitored in the study include body weight, food consumption, water intake, hematology, urinalysis, serum biochemistries, and gross and microscopic pathology. Terminal body weights of male and female rats fed 5% diethyl phthalate and female rats fed 1% diethyl phthalate were reduced significantly in comparison with controls. Paired feeding studies indicated that these reductions were not due to decreased food consumption. In comparison with controls, statistically significant decreases in absolute organ weights (brain, heart, spleen, kidneys) and increases in relative organ weights (brain, liver, stomach, small intestine, full calcium, testes, kidneys) were observed in males and females fed 5.0% diethyl phthalate for 16 weeks. These changes were attributed to the compound-related effect on growth rate since dose-related changes in gross or microscopic pathology were observed. No other effects were observed.

5.5.3. **Di-n-butyl Phthalate.** The oral toxicity of di-n-butyl phthalate has been tested in rats (Smith, 1953; Nikonorow et al., 1973; Maslenko, 1968; Lefaux, 1968; Piekacz, 1971; LeBreton, n.d.; Bornmann et al., 1956) and mice (Ota et al., 1974). These studies are summarized in Table 5-9. The only investigators who reported effects are Smith (1953), Ota et al. (1974) and Nikonorow et al. (1973).

Smith (1953) fed either 0, 0.01, 0.05, 0.25, or 1.25% di-n-butyl phthalate in the diet to groups of 10 male Sprague-Dawley rats for 1 year. Equivalent doses using a factor of 5% are 0, 5, 25, 125 or 625 mg/kg/day. Endpoints monitored include body weight, food consumption, hematology and gross and microscopic pathology. The only effect observed was 50% mortality during the first week of the study among rats fed 1.25% di-n-butyl phthalate.

Increased relative liver weight in the absence of histopathological liver lesions were observed in rats treated with 120 or 1200 mg/kg/day for 3 months (Nikonorow et al., 1973). Degenerative changes in the kidneys and liver were reported to occur in mice fed 500 or 5000 mg di-n-butyl phthalate/kg/day in the diet for 1-3 months (Ota et al., 1974). No other details were given.

5.5.4. **Dimethyl Phthalate.** Lehman (1955) fed groups of rats (number, sex and strain not reported) dimethyl phthalate at levels of 2, 4 or 8% in the diet (1000, 2000 or 4000 mg/kg/day using a food factory of 0.05) for 2 years (Table 5-10). U.S. EPA (1980a) incorrectly attributed this study to Draize et al. (1948). No effects were observed among rats fed 2% dimethyl phthalate. A minor effect on growth was observed at 8%, while "nephritic involvement" (U.S. EPA, 1980a) was observed at 4 and 8%.

TABLE 5-9

Oral Toxicity Summary for Di-n-butyl Phthalate

Species/ Strain	Number and Sex	Dose, Vehicle and Duration of Treatment	Endpoints Monitored	Effects	Reference
Rat/Sprague-Dawley	10 M/group	0, 0.01, 0.05, 0.25 or 1.25% diet for 1 year	body weight, food consumption, hematology, gross and microscopic pathology (major organs)	50% mortality in first week in 1.25% group	Smith, 1953
Rat/Wistar	10 M and 10 F/group	0, 0.12 or 1.20 g/kg/day for 3 months	body weight, behavior, hematology, serum proteins, gross and microscopic examination of liver, kidney and spleen	Increased relative liver weight (0.12 and 1.20 g/kg/day); no changes in pathology of liver or other tissues	Nikonorow et al., 1973
Rat/Wistar	20 M and 20 F/group	0 or 0.125% diet for 1 year	body weight, behavior, hematology, serum proteins, gross and microscopic examination of liver, kidney and spleen	No compound-related hematological or histological changes; 4/40 and 6/40 controls and treated rats died, respectively	Nikonorow et al., 1973
Rat/Wistar	40 M and 40 F/group	0 or 1250 ppm for 7-12 months (30 rats/group killed after 7 months; the remaining rats were killed after 12 months)	body weight; kidney, liver and spleen weights; SGOT and SGPT activities	None	Piekacz, 1971
Rat/NR	NR/NR	0, 100, 300 ppm diet for 21 months	NR	None	LeBreton, n.d.
Rat/NR	NR/NR	500 ppm diet for 15 months; 500 or 1000 mg/kg (2 times/week) by gavage (vehicle NR) for 1 year	NR	None	Bornmann et al., 1956
Rat/NR	NR/NR	2.5 mg/kg/day for 6 months (vehicle NR)	NR	None	Maslenko, 1968
Rat/NR	NR/NR	100 mg/kg/day for 21 months or 5 generations; 300 mg/kg/day for 21 months or 3 generations; 500 mg/kg/day for 15 months or 3 generations	NR	"No carcinogenic or poisonous effects"	Lefaux, 1968
Mouse/NR	NR/NR	0.5, 5 g/kg/day diet for 1-3 months	NR	Degenerative changes in kidney and liver	Ota et al., 1974

NR = Not reported

TABLE 5-10

Oral Toxicity Summary for Miscellaneous Phthalate Esters

Ester	Species/ Strain	Number and Sex	Dose, Vehicle and Duration of Treatment	Endpoints Monitored	Effects	Reference
Dimethyl phthalate	rat/NR	NR/NR	2, 4 or 8% diet for 2 years	NR	"Minor" effect on growth at 4 and 8%; "some indication of nephritic involvement" at 8%	Lehman, 1955*
Diisononyl phthalate	rat/NR	M and F (numbers NR)	0, 50, 150, 500 mg/kg/day for 13 weeks (vehicle NR)	NR	(50, 150 mg/kg/day) no effects (500 mg/kg/day) slight reduction in growth rate, increased liver weight (NOS)	Livingston, 1971
	dog/NR	4 M and F (not clear whether 4 dogs/group or 4 dogs total; appears to be 4 dogs total)	0, 0.125, 0.500% for 13 weeks; 2% for 8 weeks then increased to 4% for remaining 5 weeks (TWA = 2.8%)	NR	(0.125%) no effect; (0.5%) questionable increased liver weight (NOS); (2.8%) decreased body weight; increased liver weight, histological changes in liver, gall bladder, spleen and kidney	Livingston, 1971
n-Butyl benzyl phthalate	rat/NR	NR, NR	0, 0.25, 0.5, 1.0, 1.5 or 2.0% diet for 90 days	growth, hematology, urinalysis, gross and microscopic pathology	0.25-0.5%; no effects; (1.50%) slightly reduced growth rate; (2.0%) slightly reduced growth rate; increased liver weight (1-2.0%) but no histopathological changes were observed	Monsanto, 1972
	rat/F344	50 M, 50 F/ group	0, 6000 or 12,000 ppm diet for 103 weeks (females) or 28 weeks (males)	body weight, food consumption, mortality, clinical signs of toxicity, gross and microscopic pathology	Increased mortality associated with "unexplained internal hemorrhaging" in treated male rats only; slightly reduced body weight in treated females accompanied by reduction in food consumption	NTP, 1982a
	mouse/ B6C3F1	50 M, 50 F/ group	0, 3000 or 6000 ppm diet for 103 weeks	body weight, mortality, clinical signs of toxicity, gross and microscopic pathology	Reduced body weight in treated males and females; no data on food consumption	NTP, 1982a
n-Butyl benzyl phthalate	dog/NR	NR/NR	0, 1, 2 or 5% diet in capsule form for 90 days	weight gain, mortality, food consumption, hematology, urinalysis, liver and kidney function	Initial reduction in body weight due to refusal to eat (5% group only)	Monsanto, 1972

TABLE 5-10 (cont.)

Ester	Species/ Strain	Number and Sex	Dose, Vehicle and Duration of Treatment	Endpoints Monitored	Effects	Reference
Di-n-octyl phthalate	rat/ Wistar	40 M and 40 F/group	0 or 3500 ppm diet for 7-12 months (30 rats killed after 7 months; remainder killed after 12 months)	body weight; kidney, liver and spleen weights; SGOT and SGPT activities	Elevated relative liver weight (females at 7 and 12 months); elevated relative kidney weight (females at 12 months); significantly elevated SGOT and SGPT (males and females at 12 months)	Piekacz, 1971
	mouse/	pairs of 20 M and F/group	1.25, 2.5 or 5% in diet for 2 generations	number of litters/pair, % pups born alive, live pup weight, weight at weaning, mating behavior, reproductive performance, sperm counts	None	Gulati et al., 1985

*U.S. EPA (1980b) incorrectly attributed these data to Draize et al. (1948)

NR = Not reported; NOS = not otherwise specified

5.5.5. Diisononyl Phthalate. Livingston (1971) exposed rats and dogs orally (method not specified) to diisononyl phthalate for 13 weeks (see Table 5-10). Male and female rats (strain, numbers not reported) were given 0, 50, 150 or 500 mg/kg/day. No effects were observed among low- and middle-dose rats. Increased liver weight and a slight reduction in growth rate were observed among high-dose rats. Dogs were given 0, 0.125 or 0.5% dimethyl phthalate for 13 weeks, or 2% for 8 weeks followed by 4% for 5 weeks (TWA 2.8%). Dogs given a TWA concentration of 2.8% dimethyl phthalate had decreased body weights, increased liver weights, and histological changes in the liver, gall bladder, spleen and kidneys. Assuming a dog consumes a daily amount of food equal to 2.5% of its body weight (Durkin, 1985), the TWA concentration is equivalent to 700 mg/kg/day. No effects were observed among low-dose dogs (31.25 mg/kg/day), but middle-dose (125 mg/kg/day) dogs had increased liver weights.

5.5.6. n-Butyl Benzyl Phthalate. NTP (1982a) fed n-butyl benzyl phthalate to female F344 rats at concentrations of 0, 6000 or 12,000 ppm and B6C3F1 mice of both sexes at concentrations of 0, 3000 or 6000 ppm (see Section 5.1. for doses) for 103 weeks. The only noncarcinogenic effects observed in female rats and male and female mice were reductions in growth rate (see Table 5-10). Growth rate reduction in female rats was accompanied by reduced food consumption. Data on food consumption were not reported for mice. Male F344 rats were also fed 0, 6000 or 12,000 ppm n-butyl benzyl phthalate, but the study was terminated after 28 weeks because of high mortality among treated rats. Mortality was attributed to unexplained hemorrhaging.

Krauskopf (1973) reported 90-day feeding studies on rats and dogs (strains, sex, numbers not reported) conducted by Monsanto (1972). Rats were fed 0, 0.25, 0.5, 1.0, 1.5 or 2% (0, 125, 250, 500, 750 or 1000 mg/kg/day, assuming a food factor of 0.05) n-butyl benzyl phthalate, while dogs were fed 0, 1, 2 or 5% (0, 250, 500 or 1250 mg/kg/day, assuming a food factor of 0.025) n-butyl benzyl phthalate. No adverse effects were observed among dogs fed n-butyl benzyl phthalate at any level, or among rats fed 0.25 or 0.5% n-butyl benzyl phthalate. Increased liver weights without accompanying histopathological changes were observed among rats fed 1-2% n-butyl benzyl phthalate. Slightly reduced growth rate was observed at the two highest doses. In a draft report, NTP (1985) conducted a toxicity and mating trial study in F344 rats concomitantly. The toxicity portion of this report was conducted to determine the no toxic effect level and to evaluate the dose response of BBP. Rats were administered concentrations of either 0, 0.03, 0.09, 0.28, 0.83 or 2.50% BBP in the diet for 26 weeks. There were 15 male animals in each dose group, starting at 6 weeks of age. Throughout the study, body weight gain was significantly depressed at the 2.5% BBP level when compared with the controls. There were no deaths attributed to BBP toxicity. All the rats given 2.5% BBP had small testes upon gross necropsy at the 26-week termination. Five of 11 had soft testes and only 1/11 had a small prostate and seminal vesicle. In the 0.03, 0.09, 0.28 and 0.83% BBP dose groups there were no grossly observable effects on male reproductive organs. The kidneys of six animals in the 2.5% group contained focal cortical areas of infarct-like atrophy. In addition, testicular lesions were also observed at the 2.5% dose level. Lesions were characterized by atrophy of seminiferous tubules and aspermia. The other treatment groups showed no evidence of abnormal morphology in any other organs.

Histopathological changes were also seen at the 2.5% BBP level after 10 weeks of exposure in the mating trial portion of this study. After histopathological examination, testicular lesions were characterized by atrophy of seminiferous tubules and a near total absence of mature sperm production. When 10/30 females successfully mated with the 2.5% treatment level males, none were pregnant at necropsy. The investigators concluded that the data suggest a depression in male reproductive organ weights by either a direct or indirect toxic effect after 2.5% BBP administration. BBP at 0.83% in the diet did not result in any treatment-related effects as evaluated by the authors. The investigators concluded from the results of both studies that a threshold for toxicity would be between 0.83 and 2.5% BBP.

In contrast to the author's conclusions, some alterations in animals fed 0.83% BBP were noted which may have been compound related in that they occurred in the 2.5% group also, but not in lower exposure groups. Liver-to-body weight ratios were significantly increased in both the 0.83 and 2.5% diet groups, while liver-to-brain weight ratio was increased in the 0.83% group alone. Absolute liver weight was also increased in the 0.83% group. Hematological evaluations showed small but significant elevations in mean corpuscular hemoglobin in the 0.83% group at 60, 90, 120 and 150 days, but not at 30 or 180 days, while mean corpuscular hemoglobin concentration was increased at 60 and 120 days. Interestingly, no alterations in these parameters was seen in the lower dose groups. The 2.5% group showed a consistent pattern of increased reticulocytes, decreased red blood cells, increased mean corpuscular volume, increased mean corpuscular hemoglobin and hemoglobin concentration in addition to reduced cellularity of the bone marrow.

5.5.7. **Di-n-octyl Phthalate.** A Polish abstract (Piekacz, 1971) reports that groups of 40 male and female rats (strain not reported) were fed either 0 or 3500 ppm (0 or 175 mg/kg/day, using a food factor of 0.05) di-n-octyl phthalate in the diet for 7-12 months. Elevated relative liver weight was observed among di-n-octyl phthalate-treated females at 7 and 12 months. SGOT and SGPT were significantly increased in both males and females at 12 months. Increased kidney weight was reported among females at 12 months. Effects on spleen weight or body weight were not observed. Histopathological examination was apparently not performed.

5.5.8. **Human Studies.** The health status of 147 workers who handled phthalate plasticizers was evaluated by Milkov et al. (1973). Workers were exposed to a mixture of compounds including di-n-butyl phthalate, DAP-789, di-n-octyl phthalate, diisooctyl phthalate, n-butyl benzyl phthalate, selacinates, adipinates, vinyl chloride, carbon monoxide amd mixed ethers. Phthalate exposure was estimated to be 1-40 mg/m³. Effects attributed to phthalate exposure included polyneuritis (frequency and intensity increased with duration of employment), decline in vestibular and olfactory excitability and reductions in thrombocytes, leukocytes, hemoglobin and "blood color index."

Gilioli et al. (1978) performed clinical neurological electromyographic and electroneurologic tests on 38 workers in the phthalate plasticizer industry. Of the 38 workers, 23 had been exposed only to phthalate esters (not otherwise specified) for an average of 4.5 years; the remainder had been exposed only to alcohols or only to phthalic anhydride. Ambient concentrations of phthalate esters were <1-5 mg/m³ in some areas and 5-60 mg/m³ in others. Of the 23 workers exposed only to phthalate esters, 12 were found to have mild to moderate polyneuropathy of the sensory-motor and motor types. The frequency and severity increased with length of exposure; no cases were found in workers exposed for <2 years.

Aldyreva et al. (1974) reported an increase in the incidence of miscarriages and menstrual disorders among women exposed to phthalate esters in the synthetic leather industry. Details concerning the exposed and control populations were not given. Thiess et al. (1978) examined morbidity among 101 workers employed in the production of di(2-ethylhexyl) phthalate for an average of 12 years (range=4 months to 35 years). Exposure ranged from 0.0006-0.01 ppm (0.01-0.16 mg/m^3). There was no evidence of a higher incidence of miscarriages or deformities of offspring among female workers or the wives of male workers. No other compound-related effects were observed, though di(2-ethylhexyl) phthalate was found in the blood and urine of both exposed and control groups.

5.6. OTHER RELEVANT INFORMATION

Acute oral toxicities for phthalate esters are summarized in Table 5-11.

5.7. SUMMARY

Di(2-ethylhexyl) and n-butyl benzyl phthalates have been tested for carcinogenic potential in feeding studies with F344 rats and B6C3F1 mice. Di(2-ethylhexyl) phthalate was found to cause increased incidences of liver neoplasms in both rats and mice (NTP, 1982b; Kluwe et al., 1982b). n-Butyl benzyl phthalate caused an increase in myelomonocytic leukemia in female F344 rats (NTP, 1982a). Because of high background incidence of myelomonocytic leukemia in F344 rats and because dose-related and significant decreases in malignant lymphoma, all lymphoma, and leukemia or lymphoma were observed in male B6C3F1 mice (NTP, 1982a), there is only limited evidence to conclude that n-butyl benzyl phthalate is carcinogenic.

TABLE 5-11

Acute Oral Toxicity of Phthalate Esters

Phthalate Ester	Species	LD_{50}	Reference
Di(2-ethylhexyl)	rat	26 g/kg	Krauskopf, 1973
	rabbit	33.9 g/kg	Shaffer et al., 1945
	guinea pig	26.3 g/kg	Krauskopf, 1973
	mouse	33.5 g/kg	Krauskopf, 1973
Dimethyl	rat	6.9 mℓ/kg	Draize et al., 1948
	mouse	7.2 mℓ/kg	Draize et al., 1948
	rabbit	4.4 mℓ/kg	Draize et al., 1948
	guinea pig	2.4 mℓ/kg	Draize et al., 1948
Diethyl	rat	8.2 mℓ/kg	Krauskopf, 1973
	rabbit	1.0 g/kg	Sandermeyer and Kirwin, 1981
Dibutyl	rat	23.0 g/kg	Radeva and Dinoeva, 1966; Gesler, 1973
		12.5 g/kg	Homrowski and Nikonorow, 1959; Nikonorow et al., 1973
		14.95 g/kg	Komarova, 1979
		~8 g/kg	Smith, 1953
		>20 mℓ/kg	Lehman, 1955
	mouse	9 g/kg	Komarova, 1979
	mouse (M)	14.8-17.0	Omori, 1976; Yamada et al., 1975
	mouse (M)	9.77 g/kg	Miyahara et al., 1973; Omori, 1976
n-Butyl benzyl	rat (M&F)	2.33 g/kg	NTP, 1982a
	mouse (M)	6.16 g/kg	NTP, 1982a
	mouse (F)	4.17 g/kg	NTP, 1982a
Di-n-octyl	rat	>13 g/kg	Sandermeyer and Kirwin, 1981
Dihexyl	rat	29.6 g/kg	Sandermeyer and Kirwin, 1981
Dinonyl	rat	>2 g/kg	Sandermeyer and Kirwin, 1981
Didecyl	rat	>64 g/kg	Sandermeyer and Kirwin, 1981

The mutagenicity and genotoxicity of phthalic acid esters have been reviewed by Thomas and Thomas (1984) and Hopkins (1983). Di-2(ethylhexyl) phthalate and metabolites have yielded mostly negative results in Ames tests with _S_. _typhimurium_, and mixed results with _in vitro_ and _in vivo_ tests of genotoxicity. Diethyl phthalate, dimethyl phthalate, and di-n-butyl phthalate were found to be mutagenic in _in vitro_ microbial assays with _S_. _typhimurium_ (Kozumbo et al., 1982; Rubin et al., 1979; Seed, 1982).

Oral studies have shown that di(2-ethylhexyl) phthalate, di-n-butyl phthalate, and di-n-heptyl phthalate can produce adverse effects upon the developing fetus when mice and rats are exposed during gestation (Wolkowski-Tyl, 1984a,b; Bell et al., 1979; Bell, 1980; Shiota and Mima, 1985; Shiota and Nishimura, 1982; Shiota et al., 1980; Nakamura et al., 1979; Yagi et al., 1978, 1980; Tomita et al., 1982b; Onda et al., 1974). Whether the observed effects (reduced fetal weight, fetal mortality, gross external and skeletal malformations) represent a primary effect of the compound in question or whether they occur as a result of maternal toxicity has yet to be demonstrated unequivocally. Studies conducted by NTP (Wolkowski-Tyl et al., 1984a,b) indicate that mice are more sensitive than rats.

NTP has recently conducted reproduction and fertility assessments on CD-1 mice for diethyl phthalate (Reel et al., 1984) and di-n-octyl phthalate (Gulati et al., 1985). Dietary di-n-octyl phthalate had no effects on reproduction and fertility among parental or F_1 mice. Dietary diethyl phthalate had no effects on reproduction and fertility in parental mice, but diethyl phthalate-exposed F_1 mice had fewer pups/litter than did controls, as well as increased liver weights (males and females), increased prostate weights, increased pituitary weights (females only) and decreased sperm concentrations. Booth et al. (1983) and Plasterer et al. (1985) reported that dimethyl phthalate had no effects on reproduction in CD-1 mice.

Dimethyl phthalate was administered by gavage on days 7-15 of gestation. The fertility of Sherman rats was not affected by dietary administration of di(2-ethylhexyl) phthalate (up to 0.4%) for 1-2 years (Carpenter et al., 1953).

Orally administered di(2-ethylhexyl), di-n-butyl, n-butyl benzyl, di-n-pentyl, diisobutyl and di-n-heptyl phthalates have been shown to cause testicular atrophy in rats to mice (Gray et al., 1977, 1982; Shaffer et al., 1945; Gangolli, 1982; Oishi and Hiraga, 1980a, 1983; Gray and Butterworth, 1980; Mangham et al., 1981; Oishi, 1985; Agarwal et al., 1985; Foster et al., 1980). Di-n-octyl, dimethyl, diethyl, dipropyl and di-n-heptyl phthalates did not cause testicular atrophy in rats (Gray and Butterworth, 1980; Foster et al., 1980). Species differences in phthalic acid ester-promoted testicular atrophy have been observed. Gray et al. (1982) failed to observe testicular atrophy in hamsters gavaged with di-n-butyl, di(2-ethylhexyl) and di-n-pentyl phthalates at doses equimolar to those that caused atrophy in rats. In the same study, mice gavaged with equimolar doses of di-n-butyl, di(2-ethylhexyl) and di-n-pentyl phthalates had only slight focal atrophy.

Chronic or subchronic oral studies have been conducted with di(2-ethylhexyl), di-n-butyl, dimethyl, diisononyl, n-butyl benzyl and di-n-octyl phthalates (Carpenter et al., 1953; Harris et al., 1955; Nikonorow et al., 1973; Gray et al., 1977; Gangolli, 1982; NTP, 1982a,b; Kluwe et al., 1982b; Shaffer et al., 1945; Popp et al., 1985; Ganning et al., 1985; Nagasaki et al., 1974; Ota et al., 1974; Lake et al., 1976, 1977a; Maslenko, 1968; Food Research Laboratories, 1955; Brown et al., 1978; Smith, 1953; Lefaux, 1968; Piekacz, 1971; LeBreton, n.d.; Bornmann et al., 1956; Lehman, 1955; Livingston, 1971; Monsanto, 1972). Liver, kidneys and testes appear to be target organs. Occupational exposure to phthalate esters has been associated wih polyneuropathy (Milkov et al., 1973; Gilioli et al., 1978).

Acute oral LD_{50}s have been reported for di(2-ethylhexyl), dimethyl, di-n-butyl, diethyl, n-butyl benzyl, di-n-octyl, dihexyl, dinonyl and didecyl phthalates. These values are summarized in Table 5-11.

6. AQUATIC TOXICITY

Many aquatic toxicity tests with phthalate esters have used concentrations greater than the aqueous solubility of these compounds. In these cases, it is necessary to determine if toxic effects occur at concentrations that are environmentally plausible. Some investigators have used carriers or solvents to dispense or emulsify phthalate esters in water, and thus may have influenced toxicity by increasing phthalate availability. Furthermore, the carriers or solvents may have toxic effects of their own (Sugatt and Foote, 1981).

Another concern in interpreting the results of aquatic toxicity tests is that some phthalate esters (such as n-butyl benzyl and di-n-butyl phthalates) are rapidly biodegraded in natural waters ($t_{1/2}$ <2 days); such exposure conditions could change significantly during a 96-hour static bioassay. Of 32 acute toxicity studies with phthalate esters reviewed by Sugatt and Foote (1981), 28 were static exposures, and all results were based on nominal rather than measured concentrations. This illustrates the need for caution in applying these results to environmental situations.

6.1. ACUTE

Data concerning the acute toxicity of phthalate esters to aquatic vertebrates and invertebrates are presented in Tables 6-1 and 6-2, respectively. The ranges of acute LC_{50} or EC_{50} values in the various phthalate esters are presented in Table 6-3. Four of the esters had LC_{50} values for only one species. The other esters had a fairly wide range of values. Ten of the esters had LC_{50} or EC_{50} values <10 mg/ℓ in at least one species. Six of the esters were acutely toxic at concentrations of ≤1.0 mg/ℓ.

TABLE 6-1

Acute Toxicity of Phthalic Acid Esters to Aquatic Vertebrates

Species	Chemical	Toxic Concentration (mg/ℓ)	NOEC (mg/ℓ)	Effect Measured	Reference
				FRESHWATER SPECIES	
Fathead minnow *Pimephales promelas*	BBP	2.1	1.0	96-hour LC_{50} hardwater	Gledhill et al., 1980
		2.25	<1.06	14-day LC_{50}, flowthrough exposure	Gledhill et al., 1980
		2.32	NR	96-hour LC_{50}, flowthrough exposure	Gledhill et al., 1980
		5.3	2.2	96-hour LC_{50} softwater	Gledhill et al., 1980
	DBP	1.0-1.8	0.56	reduced egg hatchability and larval survival	McCarthy et al., 1985
		1.30	NR	96-hour LC_{50}	Mayer and Sanders, 1973
		2.02	NR	LC_{50}, newly hatched larvae	McCarthy and Whitmore, 1985
	DOP	10	3.2	reduced egg hatchability	McCarthy et al., 1985
	DUP	>1000	NR	96-hour LC_{50}	ABC, 1979a
	S-790^{a}	1000	NR	0-10% mortality, 96-hour	ABC, 1979b
Golden orfe *Leuciscus idus melanotus*	DAP	0.4	0.3	48-hour LC_{50}	Juhnke and Luedemann, 1978
	DEP	61	11	48-hour LC_{50}, lab 1	Juhnke and Luedemann, 1978
Goldfish *Carassius auratus*	BBP	200	100	heart rate depression	Pfuderer and Francis, 1975
	DBP	1-12	0.5	dose-related depression of heart rate	Pfuderer and Francis, 1975
	DEHP	NR	200	heart rate depression	Pfuderer and Francis, 1975
	DOP	200^{b}	NR	LC_{50}, embryo-larval stages	Birge et al., 1979
Rainbow trout *Salmo gairdneri*	BBP	3.3	<0.36	96-hour LC_{50}	Gledhill et al., 1980
	DBP	1.2-1.8	>0.5, <2.0	96-hour LC_{50}	Hrudey et al., 1976
		2.6	NR	96-hour LC_{50}	Johnson and Finley, 1980
		6.47	NR	96-hour LC_{50}	Mayer and Sanders, 1973
	DEHP	>100	NR	96-hour LC_{50}	Johnson and Finley, 1980
		540	230	96-hour LC_{50}	Hrudey et al., 1976

TABLE 6-1 (cont.)

Species	Chemical	Toxic Concentration (mg/ℓ)	NOEC (mg/ℓ)	Effect Measured	Reference
FRESHWATER SPECIES (cont.)					
Rainbow trout __Salmo gairdneri__	DOP	NR	1000	48-hour survival	Silvo, 1974
		139.1	>71.87, <148.2	22-day LC_{50} at water hardness of 50 mg/ℓ $CaCO_3$, embryos exposed from fertilization through hatching, flowthrough	Birge et al., 1978
		139.5	>55.3, <71.87	26-day LC_{50} at water hardness of 50 mg/ℓ $CaCO_3$, embryos exposed from fertilization through 4 days after hatching, flowthrough	Birge et al., 1978
		149.2	>0.5, <48.9	26-day LC_{50} at water hardness of 200 mg/ℓ $CaCO_3$, embryos exposed from fetilization through 4 days after hatching, flowthrough	Birge et al., 1978
		154.0	>0.5, <48.9	22-day LC_{50} at water hardness of 200 mg/ℓ $CaCO_3$, embryos exposed from fetilization through hatching, flowthrough	Birge et al., 1978
	DUP	>1000	NR	96-hour LC_{50}	ABC, 1979c
	S-790[a]	>1000	1000	96-hour LC_{50}	ABC, 1979d
Coho salmon __Oncorhynchus kisutch__	DEHP	>100	NR	96-hour LC_{50}	Johnson and Finley, 1980
Channel catfish __Ictalurus punctatus__	DBP	2.91	NR	96-hour LC_{50}	Mayer and Sanders, 1973
	DEHP	>100	NR	96-hour LC_{50}	Johnson and Finley, 1980
	DIMP	0.42	>0.01, <0.10	7-day LC_{50} of embryos exposed from fertilization through 4 days after hatching	Birge et al., 1978
		0.87	>0.1, <1.0	3-day LC_{50} of embryos exposed from fertilization to hatching	Birge et al., 1978
	DOP	0.69	>0.01, <0.1	7-day LC_{50} of embryos exposed from fertilization through 4 days after hatching	Birge et al., 1978
		1.21	>0.01, <0.1	3-day LC_{50} of embryos exposed from fertilization to hatching	Birge et al., 1978

TABLE 6-1 (cont.)

Species	Chemical	Toxic Concentration (mg/ℓ)	NOEC (mg/ℓ)	Effect Measured	Reference
			FRESHWATER SPECIES (cont.)		
Bluegill sunfish *Lepomis macrochirus*	BBP	1.7	0.36	96-hour LC_{50}	Gledhill et al., 1980
		43.3	22	96-hour LC_{50}	U.S. EPA, 1978c
	DBP	0.73	NR	96-hour LC_{50}	Mayer and Sanders, 1973
		1.22	NR	96-hour LC_{50}	Buccafusco et al., 1981
	DEHP	>100	NR	96-hour LC_{50}	Johnson and Finley, 1980
		>770	770	96-hour LC_{50}	U.S. EPA, 1978c
	DEP	98.2	<6.8	96-hour LC_{50}	U.S. EPA, 1978c
		110	NR	96-hour LC_{50}	Buccafusco et al., 1981
	DMP	49.5	<13	96-hour LC_{50}	U.S. EPA, 1978c
Redear sunfish *Lepomis microlophus*	DINP	4.67	>0.1-<1.0	7- to 8-day LC_{50} of embryos exposed from fertilization through 4 days after hatching	Birge et al., 1978
		71.9	>0.1-<1.0	3- to 4-day LC_{50} of embryos exposed from fertilization to hatching	Birge et al., 1978
	DOP	6.18	>0.1-<1.0	7- to 8-day LC_{50} of embryos exposed from fertilization through 4 days after hatching	Birge et al., 1978
		77.2	>0.1-<1.0	3- to 4-day LC_{50} of embryos exposed from fertilization to hatching	Birge et al., 1978
Largemouth bass *Micropterus salmoides*	DOP	32.9	>0.3, <35.5	7- to 8-day LC_{50} of embryos from fertilization through 4 days after hatching, hardwater	Birge et al., 1978
		42.1	>0.3, <46.3	7- to 8-day LC_{50} of embryos from fertilization through 4 days after hatching, softwater	Birge et al., 1978
		63.9	>0.3, <46.3	3- to 4-day LC_{50} of embryos from fertilization to hatching, softwater	Birge et al., 1978
		66.1	>0.3, <35.5	3- to 4-day LC_{50} of embryos from fertilization to hatching, hardwater	Birge et al., 1978

TABLE 6-1 (cont.)

Species	Chemical	Toxic Concentration (mg/ℓ)	NOEC (mg/ℓ)	Effect Measured	Reference
			FRESHWATER SPECIES (cont.)		
Perch *Perca fluviatilis*	DOP	NR	>saturation	3- to 4-day survival	Mehring, 1966
Roach *Rutilus rutilus*	DOP	NR	>saturation	3- to 4-day survival	Mehring, 1966
Leopard frog *Rana pipiens*	DINP	3.63	>0.1, <1.0	7- to 8-day LC_{50} of embryos exposed from fertilization through 4 days after hatching	Birge et al., 1978
		4.94	>0.1, <1.0	3- to 4-day LC_{50} of embryos exposed from fertilization to hatching	Birge et al., 1978
	DOP	4.44	>0.1, <1.0	7- to 8-day LC_{50} of embryos exposed from fertilization through 4 days after hatching	Birge et al., 1978
		5.52	>0.1, <1.0	3- to 4-day LC_{50} of embryos exposed from fertilization to hatching	Birge et al., 1978
Fowler's toad *Bufo fowleri*	DINP	2.95	>0.1, <1.0	7- to 8-day LC_{50} of embryos exposed from fertilization through 4 days after hatching	Birge et al., 1978
		23.51	>0.1, <1.0	3- to 4-day LC_{50} of embryos exposed from fertilization to hatching	Birge et al., 1978
	DOP	3.88	>0.1, <1.0	7- to 8-day LC_{50} of embryos exposed from fertilization through 4 days after hatching	Birge et al., 1978
		44.14	>0.1, <1.0	3- to 4-day LC_{50} of embryos exposed from fertilization to hatching	Birge et al., 1978
			SALTWATER SPECIES		
Bleak *Alburnus alburnus*	DMP	100-115	NR	96-hour LC_{50}, brackish water (7 ppth salinity)	Linden et al., 1979

TABLE 6-1 (cont.)

Species	Chemical	Toxic Concentration (mg/ℓ)	NOEC (mg/ℓ)	Effect Measured	Reference
			SALTWATER SPECIES (cont.)		
Sheepshead minnow *Cyprinodon variegatus*	BBP	3.0	1.0	96-hour LC_{50}	Gledhill et al., 1980
		378	355	96-hour LC_{50}	U.S. EPA, 1978c
		440	360	96-hour LC_{50}	Heitmuller et al., 1981
	DEHP	>550	550	96-hour LC_{50}	Heitmuller et al., 1981
		>770	770	96-hour LC_{50}	U.S. EPA, 1978c
	DEP	29.6	22.2	96-hour LC_{50}	U.S. EPA, 1978c
	DMP	58.0	21.5	96-hour LC_{50}	U.S. EPA, 1978c
	S-711[b]	NR	1000	no mortality	EG&G Bionomics, 1980
Mullett *Mugil cephalus*	DEP	26	10-15	96-hour LC_{50}	Shimada et al., 1983
Shiner perch *Cymatogaster aggregata*	BBP	0.08	NR	effect on coloration	Ozretich et al., 1983
		0.24	NR	effect on schooling behavior	Ozretich et al., 1983
		0.51	NR	96-hour LC_{50}	Ozretich et al., 1983
English sole *Parophrys vetulus*	BBP	0.1	NR	sublethal effects on equilibrium and activity	Randall et al., 1983
		0.30-0.45	NR	lethal threshold	Randall et al., 1983
		0.55-0.66	NR	96-hour LC_{50}	Randall et al., 1983

[a] S-790 = di(heptyl, nonyl) phthalate (Monsanto, 1983a)

[b] S-711 = di(heptyl, nonyl, undecyl) phthalate (Monsanto, 1983b)

TABLE 6-2

Acute Toxicity of Phthalic Acid Esters to Aquatic Invertebrates

Species	Chemical	Toxic Concentration (mg/ℓ)	NOEC (mg/ℓ)	Effect Measured	Reference
			FRESHWATER SPECIES		
Protozoa *Uronema parduczi*	DAP	22	<22	20-hour toxic threshold (5% inhibition of cell multiplication)	Bringmann and Kuhn, 1980a
	DEP	48	<48	20-hour toxic threshold (5% inhibition of cell multiplication)	Bringmann and Kuhn, 1980a
Entosiphon sulcatum	DAP	13	<13	72-hour toxic threshold (5% inhibition of cell multiplication)	Bringmann and Kuhn, 1980b
	DEP	19	<19	72-hour toxic threshold (5% inhibition of cell multiplication)	Bringmann and Kuhn, 1980b
Tetrahymena pyriformis	DBP	0.05	NR	complete growth inhibition	Yoshizawa et al., 1977
	DIBP	0.05	NR	complete growth inhibition	Yoshizawa et al., 1977
Cladoceran *Daphnia magna*	BBP	1.0	NR	48-hour EC_{50}, no solvent carrier	Barera and Adams, 1983
		1.6-2.2	0.62	48-hour EC_{50}, various solvent carriers	Barera and Adams, 1983
		3.7	<1.0, <2.5	48-hour EC_{50}, lake water	Gledhill et al., 1980; Landvatter, n.d.
		2.43	<2.5	48-hour LC_{50}, river water containing natural humic acid	Landvatter, n.d.
		1.91	<1.0	48-hour LC_{50}, lake water with 250 ppm fulvic acid added	Landvatter, n.d.
		92	<36	48-hour LC_{50}	LeBlanc, 1980
Cladoceran *Daphnia magna*	BBP and DEHP (1:1 w/w mixture)	0.97	<0.15	48-hour LC_{50}, duplicate tests	Landvatter, n.d.; Monsanto, 1983d
	DAP	22	NR	24-hour EC_{50}, immobilization	Bringmann and Kuehn, 1982
	DBP	1.8	0.56	decreased fecundity	McCarthy et al., 1985
		5.2	NR	48-hour LC_{50}	McCarthy and Whitmore, 1985

TABLE 6-2 (cont.)

Species	Chemical	Toxic Concentration (mg/ℓ)	NOEC (mg/ℓ)	Effect Measured	Reference
				FRESHWATER SPECIES (cont.)	
Cladoceran *Daphnia magna*	DEHP	1.59	<1.0	48-hour LC_{50}, lake water, daphnids $\leq$96 hour-old	Landvatter, n.d.
		2.0	NR	48-hour LC_{50}	Monsanto, 1983d
		2.30	<1.0	48-hour LC_{50}, lake water, daphnids $\leq$72 hours old	Landvatter, n.d.
		3.85	<1.0	48-hour LC_{50}, lake water, daphnids of unspecified age	Landvatter, n.d.
		5.29	<1.0	48-hour LC_{50}, lake water, daphids <6 days old	Landvatter, n.d.
		8.90	<1.0	48-hour LC_{50}, lake water, daphnids 48 hours old	Landvatter, n.d.
		11	1.1	48-hour LC_{50}, daphnids $\leq$24 hours old	LeBlanc, 1980
		13.9	<1.0	48-hour LC_{50}, lake water with 250 ppm fulvic acid added, daphnids of unspecified age	Landvatter, n.d.
	DEP	41	NR	24-hour EC_{50}, immobilization	Bringmann and Kuehn, 1982
		52	10	48-hour LC_{50}	LeBlanc, 1980
Cladoceran *Daphnia magna*	DMP	33	<1.7	48-hour LC_{50}	LeBlanc, 1980
	DOP	1.0	0.32	decreased fecundity	McCarthy et al., 1985
		>10	10	48-hour LC_{50}	McCarthy and Whitmore, 1985
	DUP	15	<3.2	48-hour LC_{50}	ABC, 1979e
		16	10	48-hour EC_{50}, immobilization	Monsanto, 1983c
	S-711*	>10	<2.5	48-hour LC_{50}	Landvatter, n.d.
	S-790	0.12	<0.056	48-hour LC_{50}	ABC, 1979f
Midge larvae *Chironomus plumosus*	DBP	0.76	NR	48-hour EC_{50}, 3rd-4th instar larvae	Streufert, 1977
		4.0	NR	48-hour LC_{50}, 2nd instar larvae	Streufert, 1977
		5.46	NR	48-hour LC_{50}, 3rd-4th instar larvae	Streufert, 1977
	DEHP	>18	NR	48-hour EC_{50} and 48-hour LC_{50}	Streufert, 1977

TABLE 6-2 (cont.)

Species	Chemical	Toxic Concentration (mg/ℓ)	NOEC (mg/ℓ)	Effect Measured	Reference
			FRESHWATER SPECIES (cont.)		
Midge larvae *Paratanytarsus partherogenetica*	S-711*	>10	NR	48-hour LC_{50}	Monsanto, 1983e
Blackfly larvae *Simulium* sp.	DMP	0.7-1.0	NR	9-24% mortality, 24-hour	Gjullin et al., 1949
Scud *Gammarus pseudolimnaeus*	DBP	2.10	NR	96-hour LC_{50}	Mayer and Sanders, 1973; Sanders et al., 1973
	DEHP	>32	NR	96-hour LC_{50}	Sanders et al., 1973
Scud *Gammarus pulex*	DEHP	NR	0.4	no mortality	Shell Oil Co., 1982
Crayfish *Orconectes nais*	DBP	>10.00	NR	96-hour LC_{50}	Mayer and Sanders, 1973; Sanders et al., 1973
Nematode *Panagrellus redivivus*	DBP	NR	0.28	96-hour survival rate	Samoiloff et al., 1980
		0.028	0.0028	96-hour change in distribution of larval stages during development relative to control distribution	Samoiloff et al., 1980
			SALTWATER SPECIES		
Mysid shrimp *Mysidopsis bahia*	BBP	0.9	0.4	96-hour LC_{50}	Gledhill et al., 1980
		9.63	3.55	96-hour LC_{50}	U.S. EPA, 1978c
	DEP	7.59	3.94	96-hour LC_{50}	U.S. EPA, 1978c
	DMP	73.7	47.8	96-hour LC_{50}	U.S. EPA, 1978c
	S-711*	NR	1000	non-toxic	EG&G Bionomics, n.d.
Grass shrimp *Palaemonetes pugio*	DBP	10 ppm	1 ppm	larval mortality during 6-day exposure	Laughlin et al., 1977
	DEHP	NR	1 ppm	larval mortality during 6-day exposure	Laughlin et al., 1977
	DMP	100 ppm	10 ppm	larval mortality during 6-day exposure	Laughlin et al., 1977

TABLE 6-2 (cont.)

Species	Chemical	Toxic Concentration (mg/ℓ)	NOEC (mg/ℓ)	Effect Measured	Reference
				SALTWATER SPECIES (cont.)	
Brine shrimp __Artemia__ __salina__	DBP	5.6	NR	24-hour LC_{50}, Larvae	Hudson et al., 1978
		8.0	NR	24-hour LC_{50}	Hudson et al., 1981
		8.2	NR	24-hour survival of larvae	Sugawara, 1974b
		10.3	NR	24-hour hatching success of eggs	Sugawara, 1974b
		10 ppm	NR	72-hour hatching success of eggs	Sugawara, 1974a
	DDP	>saturation	NR	24-hour LC_{50}, larvae	Price et al., 1974
	DEP	NR	123	24-hour survival of larvae	Sugawara, 1974b
		61.5	12.2	24-hour hatching success of eggs	Sugawara, 1974b
		50 ppm	10 ppm	72-hour hatching success of eggs	Sugawara, 1974a
	DEHP	>saturation	NR	24-hour LC_{50}, larvae	Price et al., 1974
	DHP	50	NR	slight reduction in hatching success, 40-hour	Sugawara, 1974a
	DMP	NR	50 ppm	72-hour hatching success of eggs	Sugawara, 1974a
		NR	120	24-hour survival of larvae	Sugawara, 1974b
Copepod __Nitocra__ __spinipes__	DBP	1.7	NR	96-hour LC_{50}	Linden et al., 1979
	DEHP	>300	NR	96-hour LC_{50}	Linden et al., 1979
	DEP	74	NR	96-hour LC_{50}	Bengtsson and Tarkpea, 1983
	DIBP	3.0	NR	96-hour LC_{50}	Linden et al., 1979
Copepod __Nitocra__ __spinipes__	DMP	62	NR	96-hour LC_{50}	Linden et al., 1979
	DNP	>300	NR	96-hour LC_{50}	Linden et al., 1979
Mud crab __Rhithropanopeus__ __harrisii__	DBP	NR	1.0 ppm	survival, development time and abnormalities of larvae	Laughlin et al., 1977
	DMP	NR	1.0 ppm	survival, development time and abnormalities of larvae	Laughlin et al., 1977

*S-711 = di(heptyl, nonyl, undecyl) phthalate (Monsanto, 1983b)

NR = Not reported

TABLE 6-3

Range of Acute LC_{50} and EC_{50} Values for Phthalate Esters

Phthalate Ester	Solubility[a] Limit (mg/ℓ)	Range of Acute LC_{50} or EC_{50} Values (mg/ℓ or ppm)			
		Algae	Invertebrates	Fish	All Organisms
DMP	1744-5000	26.1-185 (3)[b]	7-73.4 (4)	49.5-115 (3)	7-185 (10)
DEP	210-1000	3-90.3 (3)	7.6-74 (3)	29.6-110.0 (3)	3-110.0 (9)
DAP	100	NR	22 (1)	0.4 (1)	0.4-22.0 (2)
DPP	56	0.9-65 (1)	NR	NR	0.9-6.5 (1)
DBP	<0.1-13	0.0034-0.6 (1)	1.7->10.0 (4)	0.73-6.47 (4)	0.0034->10 (9)
DIBP	6.2	NR	3.0 (1)	NR	3.0 (1)
BBP	0.71-2.9	0.11-1.0 (5)[c]	0.9-92 (2)	0.51-440.0 (4)	0.11-440 (11)[c]
DOP	3	NR	1.0->10 (2)	0.69-200.0 (7)[d]	0.69-200.0 (9)[d]
DEHP	0.285-1.3	31,000 (1)	1.6->300 (4)	540->770 (5)	1.6-31,000 (10)
DNP	NR	NR	>300 (1)	NR	>300 (1)
DINP	NR	NR	NR	0.42-71.85 (4)[d]	0.42-71.85 (4)[d]
DDP	0.33	NR	>saturation (1)	NR	>saturation (1)
DUP	NR	<360->1000 (1)	15-16 (1)	>1000 (2)	15->1000 (4)

[a] Source: Sugatt and Foote, 1981

[b] Number in parentheses is the number of species tested.

[c] One species of algae had a clearly exceptional LC_{50} of 1000 mg/ℓ.

[d] Includes two amphibian species

NR = Not reported

Because of the large variability in LC_{50} and EC_{50} values for each ester, it is difficult to draw conclusions about which esters are most acutely toxic to aquatic organisms.

6.2. CHRONIC

Data concerning chronic toxicity of phthalic acid esters to aquatic vertebrates are presented in Table 6-4. Di(2-ethylhexyl) phthalate was the ester for which there was the most data. Toxic effects were reported at concentrations as low as 0.0037 mg/ℓ in brook trout, Salvelinus fontinalis (Mayer et al., 1977). In embryo-larval tests with fathead minnows, Pimephales promelas, the order of decreasing toxicity for four esters was di(2-ethylhexyl) phthalate, n-butyl benzyl phthalate, di-n-butyl phthalate and di-n-octyl phthalate. Di(2-ethylhexyl) phthalate caused decreased collagen content of the backbones of fry exposed to concentrations of 0.011-0.100 mg/ℓ for 127 days (Mayer et al., 1977). n-butyl benzyl phthalate caused reduced growth at 0.360 mg/ℓ (Gledhill et al., 1980), while di-n-butyl phthalate and di-n-octyl phthalate affected survival and/or egg hatchability at 1.0 and 10.0 mg/ℓ, respectively (McCarthy and Whitmore, 1985).

Data concerning chronic toxicity of phthalates to aquatic invertebrates are presented in Table 6-5. Once again, di(2-ethylhexyl) phthalate appeared to be more toxic than the other esters, having inhibited reproduction of Daphnia magna at concentrations as low as 0.003 mg/ℓ (Mayer and Sanders, 1973). N-butyl benzyl phthalate, di-n-octyl phthalate and di-n-butyl phthalate were about equal in toxicity to Daphnia magna, adversely affecting reproduction at 0.76, 1.0 and 1.8 mg/ℓ, respectively (Gledhill et al., 1980; McCarthy and Whitmore, 1985).

TABLE 6-4

Chronic Toxicity of Phthalic Acid Esters to Aquatic Vertebrates

Species	Chemical	Toxic Concentration (mg/ℓ)	NOEL (mg/ℓ)	Effect Measured	Reference
			FRESHWATER SPECIES		
Rainbow trout *Salmo gairdneri*	DEHP	0.014-0.054	0.005	Decreased collagen content of backbone, 90-day exposure, eggs and fry	Mayer et al., 1977
		0.054	0.005-0.014	Mortality of sac fry, decreased protein content exposure was 12-day eggs and 90-day post-hatch	Mehrle and Mayer, 1976
		NR	0.1	No effect on growth or survival of adults, 60-day exposure	McCarthy and Whitmore, 1985
Brook trout *Salvelinus fontinalis*	DEHP	0.0037-0.052	NR	Decreased collagen content of backbone, 150-day exposure, adults	Mayer et al., 1977
Fathead minnow *Pimephales promelas*	DEHP	0.011-0.100	NR	Decreased collagen content of backbone, no effects growth, 127-day exposure, fry	Mayer et al., 1977
		NR	0.062	No effects on growth or survival, 56-day exposure, embryo-larval stages	Mehrle and Mayer, 1976
	BBP	0.36	0.14	Reduced growth, normal hatching and survival	Gledhill et al., 1980
		0.22	NR	Embryo-larval stages, exposure for 30-day post-hatch mean chronic value	U.S. EPA, 1980a; Pickering, 1983
	DBP	1.0	0.56	Effects on survival, hatching rate 20-day embryo-larval test	McCarthy and Whitmore, 1985
	DOP	10	3.2	65% decreased hatchability, no effect survival	McCarthy and Whitmore, 1985
	S-711	NR	0.001-0.265	34-Day embryo-larval test, no effects on egg hatchability, fry survival, growth 30-day exposure	Monsanto, 1983f
Frog *Xenopus laevis*	DEHP	2.0	NR	Retarded development, reduced pigmentation, 8- to 30-week exposure, tadpoles	Dumpert and Zietz, 1984

TABLE 6-5

Chronic Toxicity of Phthalic Acid Esters to Aquatic Invertebrates

Species	Chemical	Toxic Concentration (mg/ℓ)	NOEL (mg/ℓ)	Effect Measured	Reference
				FRESHWATER SPECIES	
Cladoceran *Daphnia magna*	DEHP	0.003-0.030	NR	Decreased numbers of offspring 60-83%, 21-day exposure	Mayer and Sanders, 1973
	DEHP	NR	0.100	No effects on survival or reproduction, 21-day exposure	Brown and Thompson, 1982a
	DBP	1.8	0.56	Inhibition of reproduction, decreased survival, 16-day exposure	McCarthy and Whitmore, 1985
	DOP	1.0	0.32	Inhibition of reproduction, 16-day exposure	McCarthy and Whitmore, 1985
	BBP	0.76	0.26	Reproduction impaired, decreased survival of second generation	Gledhill et al., 1980
	DIDP	NR	0.100	No effects on survival or reproduction, 21-day exposure	Brown and Thompson, 1982a
	DUP	16.0	11.2	Growth impairment, 7-day exposure	Monsanto, 1983c
		11.96	7.6	Impairment of growth and reproduction, 21-day exposure	Monsanto, 1983c
	S-711	2.52	1.29	Decreased survival, no effects on growth or reproduction 21-day exposure	Monsanto, 1983b
	S-790	0.501	0.388	Decreased growth, no effects on survival or reproduction, 21-day exposure	Monsanto, 1983a
Midge larvae *Chironomus plumosus*	DEHP	NR	0.360	No effects on egg production, hatchability or emergence	Streufert et al., 1980
		NR	0.18-0.56	No effect on emergence, 30-day exposure	Streufert, 1977
				SALTWATER SPECIES	
Grass shrimp *Palaemonetes pugio*	DEHP	NR	1.0	No effects on larval survival or development	Laughlin and Neff, 1978
	DMP	100.0	NR	Decreased survival, retarded development	Laughlin and Neff, 1978
Mussel *Mytilus edulis*	DEHP	NR	0.05	No adverse effects, 28 days	Brown and Thompson, 1982b
	DIDP	NR	0.05	No adverse effects, 28 days	Brown and Thompson, 1982b
Benthic estuarine communities	DBP	0.34-3.70	0.04	Decreased numbers of species and individuals, 2-week exposures	Tagatz et al., 1983

NR = Not reported

6.3. PLANTS

Data concerning effects of phthalic acid esters on aquatic plants and bacteria are presented in Table 6-6. There are four species for which sufficient data are available to compare the toxicity of different esters. For the freshwater alga, *Selenastrum capricornutum*, n-butyl benzyl phthalate was 2-3 orders of magnitude more toxic than dimethyl and diethyl phthalates (U.S. EPA, 1978c). Diallyl phthalate was ~20 times more toxic than diethyl phthalate, which was ~50 times more toxic than n-butyl benzyl phthalate to the blue-green alga, *Microcystis aeruginosa* (Bringmann and Kuehn, 1978; Gledhill et al., 1980). Among saltwater algae, the order of decreasing toxicity of phthalates to the dinoflagellate, *Gymnodinium breve*, was di-n-butyl, diphenyl, diethyl, dimethyl and di(2-ethylhexyl) phthalates (Wilson et al., 1978). The range of toxic concentrations in this species was ~10^7 (Table 6-7). In the green alga, *Skeletonema costatum*, n-butyl benzyl phthalate was ~100 times more toxic than dimethyl and diethyl phthalates (U.S. EPA, 1978c). The difficulty in making generalizations about the relative toxicity of phthalates is illustrated by the fact that n-butyl benzyl phthalate was the most toxic of three esters to *Selenastrum* and *Skeletonema*, but was the least toxic of three esters to *Microcystis*.

6.4. RESIDUES

Pharmacokinetic information for phthalates and aquatic organisms is summarized in Table 6-7. Data from model ecosystem studies concerning phthalate ester residues are presented in Table 6-8. Monitoring data for phthalate residues in various fish species are presented in Table 6-9.

TABLE 6-6

Acute Toxicity of Phthalate Esters to Aquatic Plants and Bacteria

Species	Chemical	Toxic Concentration (mg/ℓ)	NOEC (mg/ℓ)	Effect Measured	Reference
			FRESHWATER SPECIES		
BACTERIA					
Mixed bacteria	DBP	NR	1000	growth inhibition of cultures isolated from pond hydrosoil	Johnson, 1975
	DEHP	NR	1000	growth inhibition of cultures isolated from pond hydrosoil	Johnson, 1975
Mixed microorganisms		NR	100	growth inhibition and physiological activity in flow-through hydrosoil microcosm	Mutz and Jones, 1977
Pseudomonas putida	DAP	NR	100	16-hour toxic threshold (3% inhibition of cell multiplication)	Bringmann and Kuehn, 1980b
	DEP	NR	400	16-hour toxic threshold (3% inhibition of cell multiplication)	Bringmann and Kuehn, 1980b
Pseudomonas aeruginosa	DMP	1500 ppm	1000 ppm	temporary and slight growth inhibition	Perez et al., 1976
PLANTS					
Selenastrum capricornutum	BBP	0.11	<0.07	96-hour EC_{50}, chlorophyll *a*	U.S. EPA, 1978c
		0.13	NR	96-hour EC_{50}, cell number	U.S. EPA, 1978c
		0.4	0.1	96-hour LC_{50}, cell number	Gledhill et al., 1980
	DMP	42.7	<11.9	96-hour EC_{50}, chlorophyll *a*	U.S. EPA, 1978c
		39.8	NR	96-hour EC_{50}, cell number	U.S. EPA, 1978c
Selenastrum capricornutum	DEP	90.3	<22.2	96-hour EC_{50}, chlorophyll *a*	U.S. EPA, 1978c
		85.6	NR	96-hour EC_{50}, cell number	U.S. EPA, 1978c
	DUP	>1000	<360	96-hour EC_{50}, chlorophyll *a* and cell number	EG&G Bionomics, 1979a
	S-790	>1000	<360	96-hour EC_{50}, chlorophyll *a* and cell number	EG&G Bionomics, 1979b
	S-711	>1000	NR	96-hour EC_{50}, chlorophyll *a* and cell number	EG&G Bionomics, 1978

TABLE 6-6 (cont.)

Species	Chemical	Toxic Concentration (mg/ℓ)	NOEC (mg/ℓ)	Effect Measured	Reference
FRESHWATER SPECIES (cont.)					
Microcystis aeruginosa	DAP	0.65	<0.65	8-day toxic threshold (3% inhibition of cell multiplication)	Bringmann and Kuehn, 1978
	DEP	15	<15	8-day toxic threshold (3% inhibition of cell multiplication)	Bringmann and Kuehn, 1978
	BBP	1000	560	96-hour LC_{50}, cell number	Gledhill et al., 1980
	S-711	>1000	NR	96-hour EC_{50}, chlorophyll *a* and cell number	EG&G Bionomics, 1978
Navicula pelliculosa	BBP	0.6 (0.2-2)	0.3	96-hour EC_{50}, cell number	Gledhill et al., 1980
	S-711	>1000	NR	96-hour EC_{50}, chlorophyll *a* and cell number	EG&G Bionomics, 1978
Scenedesmus quadricauda	DAP	2.9	<2.9	8-day toxic threshold (3% inhibition of cell multiplication)	Bringmann and Kuehn, 1980b
	DEP	10	<10	8-day toxic threshold (3% inhibition of cell multiplication)	Bringmann and Kuehn, 1980b
Gymnodinium breve	DBP	0.0034-0.2 ppm	NR	96-hour EC_{50}, growth rate, duplicate tests	Wilson et al., 1978
		0.02-0.6 ppm	NR	96-hour LC_{50}, cell population, duplicate tests	Wilson et al., 1978
	DPP	0.9-2.4 ppm	NR	96-hour EC_{50}, growth rate, duplicate tests	Wilson et al., 1978
		1.3-6.5 ppm	NR	96-hour LC_{50}, cell population, duplicate tests	Wilson et al., 1978
	DEP	3-6.1 ppm	NR	96-hour EC_{50}, growth rate, duplicate tests	Wilson et al., 1978
		33 ppm	NR	96-hour LC_{50}, cell population	Wilson et al., 1978
	DMP	54-96 ppm	NR	96-hour EC_{50}, growth rate, duplicate tests	Wilson et al., 1978
		125-185 ppm	NR	96-hour LC_{50}, cell population, duplicate tests	Wilson et al., 1978
	DEHP	31,000 ppm	NR	96-hour EC_{50}, growth rate	Wilson et al., 1978
		NR	100,000 ppm	96-hour LC_{50}, cell population	Wilson et al., 1978
Skeletonema costatum	BBP	0.17 (0.08-0.36)	<0.03	96-hour EC_{50}, chlorophyll *a*	U.S. EPA, 1978c
		0.19 (0.09-0.38)	NR	96-hour EC_{50}, cell number	U.S. EPA, 1978c
		0.6 (0.3-2.0)	0.1	96-hour LC_{50}, cell number	Gledhill et al., 1980
	DMP	26.1 (15.9-39.3)	<11.9	96-hour EC_{50}, chlorophyll *a*	U.S. EPA, 1978c
		29.8 (22.2-40.8)	NR	96-hour EC_{50}, cell number	U.S. EPA, 1978c

TABLE 6-6 (cont.)

Species	Chemical	Toxic Concentration (mg/ℓ)	NOEC (mg/ℓ)	Effect Measured	Reference
				FRESHWATER SPECIES (cont.)	
Skeletonema costatum	DEP	65.5 (22.3-193)	<39.4	96-hour EC_{50}, chlorophyll a	U.S. EPA, 1978c
		85.0 (56.9-124)	NR	96-hour EC_{50}, cell number	U.S. EPA, 1978c
	DBP	50% ss	20% ss	96-hour growth rate, 14 ppth salinity	Medlin, 1980
		50% ss	20% ss	96-hour growth rate, 22 ppth salinity	Medlin, 1980
		NR	50% ss	96-hour growth rate, 27 ppth salinity	Medlin, 1980
		NR	NR	96-hour growth rate, 36 ppt salinity	Medlin, 1980
	S-711	>1000	NR	96-hour EC_{50}, chlorophyll a and cell number	EG&G Bionomics, 1978
Dunaliella tertiolecta	BBP	1.0 (0.2-5)	0.3	96-hour LC_{50}, cell number	Gledhill et al., 1980
	S-711	>1000	NR	96-hour EC_{50}, chlorophyll a and cell number	EG&G Bionomics, 1978

NR = Not reported

TABLE 6-7

Data from Uptake and Elimination Studies with Phthalic Acid Esters in Aquatic Biota

Species	Chemical	Water Concentration (mg/ℓ)	Tissue	Tissue Concentration (μg/g)	BCF	Duration (days)	Depuration Half-time (days)	Reference
FRESHWATER SPECIES								
FISH								
Fathead minnow *Pimephales promelas*	DEHP	0.001-0.062	whole body	NR	886-155	56	12.2	Mayer, 1976; Mehrle and Mayer, 1976
		0.0019	whole body	NR	458	14	NR	Mayer and Sanders, 1973
Rainbow trout *Salmo gairdneri*	DEHP	NR	whole body	NR	42-113	36	NR	Mehrle and Mayer, 1976
		0.07	muscle	0.021	NR	1	NR	Melancon et al., 1977
			blood	0.142	NR	1	NR	Melancon et al., 1977
			bile	51.4	NR	1	NR	Melancon et al., 1977
			liver	0.86	NR	1	NR	Melancon et al., 1977
		0.5	bile	NR	247	1	NR	Statham et al., 1976
Mosquitofish *Gambusia affinis*	DEHP	0.1	whole body	26.5	NR	2	NR	Metcalf et al., 1973
		10.0	whole body	469	NR	2	NR	Metcalf et al., 1973
Bluegill *Lepomis macrochirus*	DBP	0.00973	whole body	NR	663	21	>1, <2	Barrows et al., 1980
	DEHP	0.0057	whole body	0.64	112	35	NR	Macek et al., 1979
		0.00582	whole body	NR	114	42	3	Barrows et al., 1980
	DEP	0.00942	whole body	NR	117	21	>1, <2	Barrows et al., 1980
	DMP	0.00874	whole body	NR	57	21	>1, <2	Barrows et al., 1980
INVERTEBRATES								
Water flea *Daphnia magna*	DBP	0.00008	whole body	NR	5000	14	NR	Sanders et al., 1973
		0.0001	whole body	0.4	NR	7	3	Sanders et al., 1973
		0.0001	whole body	0.6	6000	10	3	U.S. EPA, 1972
		0.00008	whole body	NR	400	14	NR	Mayer and Sanders, 1973
	DEHP	0.0054	whole body	2.8	518	1	NR	Macek et al., 1979
		0.0003	whole body	NR	420	7	NR	Mayer and Sanders, 1973
		0.1	whole body	18.26	NR	2	NR	Metcalf et al., 1973
		10.0	whole body	1551	NR	2	NR	Metcalf et al., 1973
		0.0003	whole body	NR	5000	7	NR	Sanders et al., 1973
		NR	whole body	NR	209	21	NR	Brown and Thompson, 1982a
	DIDP	NR	whole body	NR	116	21	NR	Brown and Thompson, 1982a
Damselfly *Ischnura verticalis*	DBP	0.0001	whole body	NR	2700	7	NR	Sanders et al., 1973

TABLE 6-7 (cont.)

Species	Chemical	Water Concentration (mg/ℓ)	Tissue	Tissue Concentration (µg/g)	BCF	Duration (days)	Depuration Half-time (days)	Reference
FRESHWATER SPECIES (cont.)								
Sowbug Asellus brevicaudus	DEHP	0.0015	whole body	NR	70	21	NR	Sanders et al., 1973
		0.062	whole body	NR	250	21	NR	Sanders et al., 1973
Midge Chironomus plumosus	DBP	0.00018	whole body	NR	720	7	NR	Mayer and Sanders, 1973
		0.00018	whole body	NR	6600	7	NR	Sanders et al., 1973
	DEHP	0.0002	whole body	NR	292	2	NR	Streufert et al., 1980
		0.0003	whole body	NR	350	7	NR	Mayer and Sanders, 1973
		0.0003	whole body	NR	3100	7	NR	Sanders et al., 1973
Mayfly Hexagenia bilineata	DBP	0.00008	whole body	NR	430	7	NR	Mayer and Sanders, 1973
		0.0001	whole body	NR	1900	7	NR	Sanders et al., 1973
	DEHP	0.0001	whole body	NR	575	7	NR	Mayer and Sanders, 1973
		0.0001	whole body	NR	2300	7	NR	Sanders et al., 1973
Scud Gammarus pseudolimnaeus	DBP	0.0001	whole body	NR	6700	NR	NR	Sanders et al., 1973
		0.0001	whole body	NR	1400	14	NR	Mayer and Sanders, 1973
	DEHP	0.063	whole body	NR	260	21	NR	Sanders et al., 1973
		0.0001	whole body	NR	3600	14	NR	Mayer and Sanders, 1973
		0.0001	whole body	NR	13,400	14	NR	Sanders et al., 1973
		0.0001	whole body	5.4	NR	3	<4	Sanders et al., 1973
Mosquito larvae Culex sp.	DEHP	0.1	whole body	16.37	NR	2	NR	Metcalf et al., 1973
		10.0	whole body	3657	NR	2	NR	Metcalf et al., 1973
Mosquito pupae Culex sp.	DEHP	0.1	whole body	2.03	NR	2	NR	Metcalf et al., 1973
		10.0	whole body	4346	NR	2	NR	Metcalf et al., 1973
Snail Physa sp.	DEHP	0.1	whole body	85.7	NR	2	NR	Metcalf et al., 1973
		10.0	whole body	487	NR	2	NR	Metcalf et al., 1973
Glass shrimp Palaemonetes kakiadensis	DBP	0.00008	whole body	NR	5000	3	NR	Sanders et al., 1973
PLANTS								
Alga Selenastrum capricornutum	DBP	NR	whole body	NR	22,700	NR	NR	Casserly et al., 1983
Plant Elodea sp.	DEHP	0.1	whole body	23.24	NR	2	NR	Metcalf et al., 1973
		10.0	whole body	290	NR	2	NR	Metcalf et al., 1973

TABLE 6-7 (cont.)

Species	Chemical	Water Concentration (mg/ℓ)	Tissue	Tissue Concentration (μg/g)	BCF	Duration (days)	Depuration Half-time (days)	Reference
SALTWATER SPECIES								
FISH								
Sheepshead minnow *Cyprinodon variegatus*	DEHP	0.06	whole body	NR	637	NR	30	Karara and Hayton, 1984
Mullet *Mugil cephalus*	DEP	10-15	whole body	NR	15-16	4	NR	Shimada et al., 1983
INVERTEBRATES								
Brine shrimp *Artemia salina*	DBP	NR	whole body	NR	2300	0.33	NR	Hudson et al., 1981
Mussel *Mytilus edulis*	DEHP	0.005 or 0.05	whole body	NR	2500	28	3.5	Brown and Thompson, 1982b
	DIDP	0.005 or 0.05	whole body	NR	3500	28	3.5	Brown and Thompson, 1982b

NR = Not reported

TABLE 6-8

Data from Model Ecosystem Studies Concerning Phthalate Residues

Species	Chemical	Water Concentration (mg/ℓ)	Tissue Concentration (µg/g)	BCF	Duration (days)	Reference
Alga	DOP	0.000064	1.8	28,500	33	Sanborn et al., 1975
Water flea (*Daphnia* sp.)	DOP	0.000064	0.16	2,600	33	Sanborn et al., 1975
Mosquito (*Culex pipiens*)	DOP	0.000064	0.59	9,400	33	Sanborn et al., 1975
Snail (*Physa* sp.)	DOP	0.000064	0.85	13,600	33	Sanborn et al., 1975
Fish (*Gambusia affinis*)	DOP	0.000064	0.59	9,400	33	Sanborn et al., 1975
Alga	DOP	0.00345	2.28	660	3	Sanborn et al., 1975
Water flea (*Daphnia* sp.)	DOP	0.00345	32.5	9,426	3	Sanborn et al., 1975
Mosquito (*Culex pipiens*)	DOP	0.00345	18.3	5,300	3	Sanborn et al., 1975
Snail (*Physa* sp.)	DOP	0.00345	1.51	438	3	Sanborn et al., 1975
Fish (*Gambusia affinis*)	DOP	0.00345	0.004	1.16	3	Sanborn et al., 1975
Alga (*Oedogonium* sp.)	DEHP	0.0078	19.1	NR	33	Metcalf et al., 1973
Snail (*Physa* sp.)	DEHP	0.0078	20.3	NR	33	Metcalf et al., 1973
Mosquito (*Culex* sp.)	DEHP	0.0078	36.6	NR	33	Metcalf et al., 1973
Fish (*Gambusia affinis*)	DEHP	0.0078	0.206	NR	33	Metcalf et al., 1973
Plant (*Menthu aquatica*)	DEHP	0.001013	18.53	18,292	27	Soedergren, 1982
Plant (*Chara chara*)	DEHP	0.001013	18.50	18,263	27	Soedergren, 1982
Planarian (*Dendrocoelum lacteum*)	DEHP	0.001013	4.15	4,097	27	Soedergren, 1982
Leech (*Helobdella* sp.)	DEHP	0.001013	2.00	1,974	27	Soedergren, 1982
Snail (*Planorbis corneus*)	DEHP	0.001013	17.70	17,473	27	Soedergren, 1982
Scud (*Gammarus pulex*)	DEHP	0.001013	25.19	24,456	27	Soedergren, 1982
Midge (*Chironomus* sp.) and Oligochaete (*Tubifex* sp.)	DEHP	0.001013	1.23	1,214	27	Soedergren, 1982
Caddisfly (*Limnephilus* sp.)	DEHP	0.001013	19.46	19,210	27	Soedergren, 1982
Alderfly (*Sialis* sp.)	DEHP	0.001013	2.30	2,271	27	Soedergren, 1982
River lamprey (*Lampetra planeri*)	DEHP	0.001013	10.70	10,563	27	Soedergren, 1982
Minnow (*Phoxinus phoxinus*)	DEHP	0.001013	0.18	178	27	Soedergren, 1982
Stickleback (*Pungitius pungitius*)	DEHP	0.001013	0.31	306	27	Soedergren, 1982

TABLE 6-9

Monitoring Data for Phthalic Acid Esters in Aquatic Organisms

Species	Chemical	Tissue Concentration (µg/g)	Location	Reference
FRESHWATER SPECIES				
Lake trout *Salvelinus namaycush*	DBP	0-3.2	Lake Superior	Swain, 1978
	DEP	0-2.0	Lake Superior	Swain, 1978
	DEHP	0-1.3	Lake Superior	Swain, 1978
Whitefish *Coregonus*	DBP	0.04-0.07	Lake Superior	Swain, 1978
	DEP	1.3-2.2	Lake Superior	Swain, 1978
	DEHP	0.4-0.7	Lake Superior	Swain, 1978
Fish (general)	DBP	0-0.5	North America	Johnson et al., 1977
	DEHP	0-3.2	North America	Johnson et al., 1977
SALTWATER SPECIES				
Herring fillets	DEHP	4.71	Atlantic Ocean - Gulf of St. Lawrence	Musial et al., 1981
Clupea harengus	DHP	17	Atlantic Ocean - Gulf of St. Lawrence	Musial et al., 1981
Mackerel fillets	DEHP	6.5	Atlantic Ocean - Gulf of St. Lawrence	Musial et al., 1981
Scomber scombris	DHP	27.2	Atlantic Ocean - Gulf of St. Lawrence	Musial et al., 1981
Cod liver	DEHP	5.19	Atlantic Ocean - Gulf of St. Lawrence	Musial et al., 1981
Gadus morhua	DHP	<0.01	Atlantic Ocean - Gulf of St. Lawrence	Musial et al., 1981
Plaice fillets	DEHP	<0.01	Atlantic Ocean - Gulf of St. Lawrence	Musial et al., 1981
Hippoglossoides platessoides	DHP	<0.01	Atlantic Ocean - Gulf of St. Lawrence	Musial et al., 1981
Redfish fillets	DEHP	<0.01	Atlantic Ocean - Gulf of St. Lawrence	Musial et al., 1981
Sebastes marinus	DHP	<0.01	Atlantic Ocean - Gulf of St. Lawrence	Musial et al., 1981

The information in these three tables indicates that phthalates in general are not strongly bioaccumulated by fishes, even though phthalates are fairly lipophilic. This is because fishes are able to metabolize and eliminate phthalates, especially di(2-ethylhexyl) phthalate, rather quickly (Soedergren, 1982). In both fish and invertebrates, di(2-ethylhexyl) phthalate was degraded to the monoester (monoethylhexyl phthalate) and then to free phthalic acid, phthalic anhydride and a variety of conjugates (Mehrle and Mayer, 1976; Sodergren, 1982). In studies with several benthic invertebrate species exposed to radiolabeled di(2-ethylhexyl) phthalate, Sodergren (1982) concluded that the capacity to metabolize and eliminate di(2-ethylhexyl) phthalate was the primary determinant of accumulation. Those species that accumulated radioactivity to the greatest extent were those that had almost all of the radioactivity still in the form of di(2-ethylhexyl) phthalate, while lower total amounts of radioactivity were found in species that had metabolized the compound to other forms.

In a 35-day study with bluegills, Lepomis macrochirus, and radiolabeled di(2-ethylhexyl) phthalate (Macek et al., 1979), food and water did not accumulate radioactivity to a greater extent than fish exposed to di(2-ethylhexyl) phthalate in water alone. Steady-state whole-body concentrations in bluegills exposed to di(2-ethylhexyl) phthalate only in the diet were ~1/3 of those in fish exposed to di(2-ethylhexyl) phthalate in water. These results suggest that di(2-ethylhexyl) phthalate uptake from water is more important than di(2-ethylhexyl) phthalate uptake from food.

6.5. SUMMARY

It is difficult to draw conclusions about the relative toxicity of phthalic acid esters to aquatic biota because of the large variability in toxicity of each ester to different species. It is also difficult to pick out those species most sensitive to phthalates; however, Table 6-10 contains the most and least sensitive species and toxic concentrations reported for each ester. All of the esters listed in Table 6-10 caused toxic effects at ≤3.2 mg/ℓ. The lowest concentration reported to cause toxic effects was 0.003 mg/ℓ di(2-ethylhexyl) phthalate, which caused decreased production of offspring by Daphnia magna (Mayer and Sanders, 1973).

Although there were large differences in species sensitivity among major taxonomic groups, none of these groups except bacteria were especially more or less sensitive than other groups. Bacteria were clearly less sensitive than other organisms to di-n-butyl, diallyl, diethyl and dimethyl phthalates (Sugatt and Foote, 1981). The available information concerning freshwater and saltwater species indicated no difference in phthalate ester toxicity between freshwater and saltwater environments.

Many investigators have reported toxic effects of phthalates at concentrations greater than their aqueous solubility; however, the data indicate that all of the phthalates except dihexyl, dinonyl, di-n-decyl and diisodecyl phthlates were toxic to at least one species at concentrations near or below their solubility (Sugatt and Foote, 1981).

Information concerning residues of phthalic acid esters in aquatic biota suggests that accumulation is determined primarily by the degree to which species can metabolize and eliminate them (Soedergren, 1982). Fish generally have a well-developed mechanism in this regard and therefore do not accumulate phthalates to a great extent.

TABLE 6-10

Range of Species Sensitivity for Algae, Invertebrates and Vertebrates to Phthalate Esters

Compound[a]	No. of Species Compared	Most Sensitive Species			Least Sensitive Species		
		Species	Toxic Concentration (mg/ℓ)	Nontoxic Concentration (mg/ℓ)	Species	Toxic Concentration (mg/ℓ)	Nontoxic Concentration (mg/ℓ)
BBP	15	algae (S. costatum)	0.03	NR	algae (M. aeruginosa)	1,000	560
DAP	6	ide (L. idus)	0.4	0.3	protozoa[b] (U. parduczi)	22	<22
DBP	18	nematode (P. redivivus)	0.028	0.0028	algae (S. costatum)	NR	50% saturated solution
DEHP	16	water flea	0.003	NR	algae (G. breve)	31,000	NR
DEP	16	algae (G. breve)	3.0	NR	brine shrimp[b] (A. salina)	NR	123
DIBP	2	protozoa (T. pyriformis)	0.05	NR	copepod (N. spinipes)	3.0	NR
DINP	4[c]	catfish (I. punctatus)	1.0	0.10	redear sunfish (L. microlophus)	10	1.0
DMP	13	water flea (D. magna)	1.7	NR	brine shrimp[b] (A. salina)	NR	120
DOP	12	catfish (I. punctatus)	0.1	0.01	rainbow trout (S. gairdneri)	NR	1000
DUP	4	water flea (D. magna)	15	<3.2	fathead minnow (P. promelas)	>1,000	NR
					rainbow trout (S. gairdneri)	>1,000	NR

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[a] Comparisons for DHP, DPP, DNP and DDP could not be made because comparable results were available for only 1 species for each ester. Comparisons for DIDP could not be made because no toxic affects occurred at any concentration tested.

[b] Bacteria were even less sensitive to these phthalate esters.

[c] Includes two amphibian species.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

RfDs have been derived for di(2-ethylhexyl) phthalate, dimethyl phthalate, diethyl phthalate, di-n-butyl phthalate, ethylphthalyl ethylglycoate, and butylphthalyl butylglycoate (U.S. EPA, 1980b). These are summarized in Table 7-1. A cancer-based water quality criterion for di(2-ethylhexyl) phthalate was derived (U.S. EPA, 1980b). A drinking water document for this class of compounds is currently in preparation.

7.2. AQUATIC

U.S. EPA (1980b) did not derive an ambient water quality criterion for the protection of aquatic life for phthalates, but did, however, note that acute and chronic toxicity to freshwater aquatic life occurred at concentrations as low as 0.940 and 0.003 mg/ℓ, respectively. For saltwater biota, U.S. EPA (1980a) noted that acute toxicity occurred at concentrations as low as 2.944 mg/ℓ, and that toxicity to one algal species occurred at 0.0034 mg/ℓ. More recent data (see Chapter 6) gave no indication of toxic effects occurring at concentrations <0.003 mg/ℓ in either freshwater or saltwater.

Earlier U.S. EPA (1972, 1976) documents recommended criteria for phthalates for the protection of aquatic life. U.S. EPA (1972) recommended a level of 0.003 mg/ℓ to protect fish and their food supply. This was based on the 0.003 mg/ℓ concentration reported to inhibit growth of *Daphnia magna* (Mayer and Sanders, 1973) and contained a safety factor of 10. U.S. EPA (1976) recommended a criteria of 0.003 mg/ℓ for freshwater aquatic life, recognizing that this concentration caused adverse effects in *Daphnia*. This level was considered acceptable because other species appeared to be much more resistant.

TABLE 7-1

Existing ADIs/RfDs for Phthalic Acid Esters from U.S. EPA, 1980b[a]

Ester	ADI (mg/kg/day)	Dose (mg/kg/day)	Species	Reference
Diethyl	13	NOEL = 1250	rat	Food Research Lab., 1955
Dibutyl	1.3	NOAEL = 125	rat	Smith, 1953
Butylphthalyl butylglycoate	10	NOEL = 1000	rat	Solver et al., 1950; Hazelton Labs., 1950
Ethylphthalyl ethylglycoate	2.5	NOEL = 250	rat	Hodge et al., 1953
Dimethyl	10	NOEL = 1000	rat	Lehman, 1955[b]

[a] These values are all currently under review and a drinking water document is currently under development.

[b] Incorrectly attributed to Draize et al. (1948) in U.S. EPA (1980b)

8. RISK ASSESSMENT

Risk assessment for phthalate esters must be performed on a compound-by-compound basis, since not all phthalic acid esters produce the same effects. For example, di(2-ethylhexyl) phthalate causes testicular atrophy, but when administered in equimolar doses, di-n-octyl phthalate does not (Gray and Butterworth, 1980; Foster et al., 1980); both compounds are 8-carbon diesters.

The following section contains assessments for di(2-ethylhexyl), diethyl, di-n-butyl, dimethyl, di-n-octyl, n-butyl benzyl and diisononyl phthalate. There were either insufficient or no available published data on chronic toxicity with which to assess the other phthalate esters covered by this document.

8.1. DI(2-ETHYLHEXYL) PHTHALATE

In lifetime feeding studies conducted by NTP (1982b), di(2-ethylhexyl) phthalate was shown to cause statistically significant increased incidences of hepatocellular carcinoma and hepatocellular carcinoma or neoplastic nodules in F344 rats dietary concentrations ≥6000 ppm and hepatocellular carcinoma and hepatocellular carcinoma or adenoma in B6C3F1 mice at dietary levels ≥3000 ppm. Based on these results, IARC (1982b) concluded that there is sufficient evidence that di(2-ethylhexyl) phthalate is carcinogenic for rats and mice. The U.S. EPA came to an equivalent conclusion. Using the EPA classification system for weight-of-evidence DEHP is a Group B2 carcinogen, meaning there is sufficient animal evidence and thus probably carcinogenic in humans. Other effects observed at low levels of exposure in oral teratogenicity and chronic studies include the following: increased relative liver weight in female guinea pigs (19 mg/kg/day) (Carpenter et al., 1953); liver and kidney congestion in a dog (79.9 mg/kg/day) (Carpenter et al., 1953); teratogenic effects in the absence of maternal toxicity in CD-1 mice (91 mg/kg/day on days 0-18 gestation) (Wolkowski-Tyl et al., 1984b); and interstitial nephritis, increased SGOT, and increased blood glucose in rats 500 ppm) (Nagasaki et al., 1974). Testicular effects were also observed in a number of studies on rats, but these effects occurred at higher levels of exposure (Gray et al., 1977, 1982; Gangolli, 1982; NTP, 1982b; Kluwe et al., 1982b; Oishi and Hiraga, 1980a, 1983; Gray and Butterworth, 1980; Mangham et al., 1981; Oishi, 1985). Doses <19 mg/kg/day have not been tested.

Using data from NTP (1982b), q_1*s were derived for combined hepatocellular carcinoma and neoplastic nodules in rats, and combined hepatocellular carcinoma and adenoma in mice (Tables 8-1 to 8-4). As seen from Tables 8-1 to 8-4, the experimental doses were multiplied by le/Le in order to expand the dose over the entire experimental period. Because the weights of the rats and mice in the different treatment groups varied, each dose was transformed to the corresponding human dose before the calculation of q_1* by multiplying the animal dose by the cube root of the ratio of the animal body weight to the reference human (70 kg) body weight. From these doses, human q_1* values were calculated directly using the computerized multistage model developed by Howe and Crump (1982); no further adjustments were necessary. The highest value, an adjusted human q_1* of 8.36×10^{-3} $(mg/kg/day)^{-1}$ (interim value as discussed later) was obtained from data on male mice. This value differs slightly from the value estimated by U.S. EPA (1980b). The 1980 value was calculated before the availability of NTP (1982) that provided estimates of doses and utilized default food consumption values. The concentrations in drinking water corresponding to risk levels of 10^{-5}, 10^{-6} and 10^{-7} are 4.19×10^{-2}, 4.19×10^{-3} and

TABLE 8-1

Cancer Data Sheet for Derivation of q_1^*

Compound: di(2-ethylhexyl) phthalate

Reference: NTP, 1982b

Species, strain, sex: rat, F344/N, male

Body weight: 0.4 kg (control); 0.36 kg (low dose); 0.32 kg (high dose)

Length of exposure (le) (weeks) = 103

Length of experiment (Le) (weeks) = 105 (0, low dose); 104 (high dose)

Lifespan of animal (L) (weeks) = 105 (0, low dose); 104 (high dose)

Tumor site and type: hepatocellular carcinoma or neoplastic nodules

Route, vehicle: oral, diet

Experimental Doses or Exposures (mg/kg/day)[a]	Transformed Dose (mg/kg/day)[b]	Incidence No. Responding/No. Examined
0	0	3/50
322	54.52	6/49
674	110.79	12/49

[a] The dietary concentrations were 0, 6000 or 12,000 ppm; the doses in mg/kg/day were provided by NTP (1982b).

[b] Dose x le/Le x $(WA/70)^{1/3}$ x $(Le/L)^3$ = transformed dose where L=Le; WA = rat body weight

Unadjusted q_1^* from study = not calculated (see text)
Human q_1^* = 2.95×10^{-3} $(mg/kg/day)^{-1}$

TABLE 8-2

Cancer Data Sheet for Derivation of q_1*

Compound: di(2-ethylhexyl) phthalate

Reference: NTP, 1982b

Species, strain, sex: rat, F344/N, female

Body weight: 0.27 kg (control); 0.26 (low dose); 0.23 kg (high dose)

Length of exposure (le) = 103 weeks

Length of experiment (Le) = 105 weeks

Lifespan of animal (L) = 105 weeks

Tumor site and type: hepatocellular carcinoma or neoplastic nodules

Route, vehicle: oral, diet

Experimental Doses or Exposures (mg/kg/day)[a]	Transformed Dose (mg/kg/day)[b]	Incidence No. Responding/No. Examined
0	0	0/50
394	59.93	6/49
774	112.88	13/50

[a] The rats were given 6000 or 12,000 ppm in the diet; the doses in mg/kg/day were provided by NTP (1982b).

[b] Dose x le/Le x $(WA/70)^{1/3}$ x $(Le/L)^3$ = transformed dose where L=Le; WA = rat body weight

Unadjusted q_1* from study = not calculated (see text)
Human q_1* = 3.52×10^{-3} $(mg/kg/day)^{-1}$

TABLE 8-3

Cancer Data Sheet for Derivation of q_1^*

Compound: di(2-ethylhexyl) phthalate

Reference: NTP, 1982b

Species, strain, sex: mouse, B6C3F1, male

Body weight: 0.04 kg (measured)

Length of exposure (le) = 103 weeks

Length of experiment (Le) = 105 weeks (0, low dose); 104 weeks (high dose)

Lifespan of animal (L) = 105 weeks (0, low dose); 104 weeks (high dose)

Tumor site and type: hepatocellular carcinoma or adenoma

Route, vehicle: oral, diet

Experimental Doses or Exposures (mg/kg/day)[a]	Transformed Dose (mg/kg/day)[b]	Incidence No. Responding/No. Examined
0	0	14/50
672	54.70	25/48
1325	108.89	29/50

[a] The mice were given 3000 or 6000 ppm in the diet; the doses in mg/kg/day were provided by NTP (1982b).

[b] Dose x le/Le x $(WA/70)^{1/3}$ x $(Le/L)^3$ = transformed dose where L=Le; WA = mouse body weight

Unadjusted q_1^* from study = not calculated (see text)
Human q_1^* = 8.36×10^{-3} $(mg/kg/day)^{-1}$

TABLE 8-4

Cancer Data Sheet for Derivation of q_1*

Compound: di(2-ethylhexyl) phthalate

Reference: NTP, 1982b

Species, strain, sex: mouse, B6C3F1, female

Body weight: 0.039 kg (control); 0.034 (low dose); 0.030 (high dose)

Length of exposure (le) = 103 weeks

Length of experiment (Le) = 105 weeks

Lifespan of animal (L) = 105 weeks

Tumor site and type: hepatocellular carcinoma or adenoma

Route, vehicle: oral, diet

Experimental Doses or Exposures (mg/kg/day)[a]	Transformed Dose (mg/kg/day)[b]	Incidence No. Responding/No. Examined
0	0	1/50
799	61.61	12/50
1821	134.68	18/50

[a] The mice were given 3000 or 6000 ppm in the diet; the doses in mg/kg/day were provided by NTP (1982b).

[b] Dose x le/Le x $(WA/70)^{1/3}$ x $(Le/L)^3$ = transformed dose where L=Le; WA = mouse body weight

Unadjusted q_1* from study = not calculated (see text)
Human q_1* = 4.73x10$^{-[illegible]}$ $(mg/kg/day)^{-1}$

4.19×10^{-4} mg/ℓ, assuming a 70 kg human consumes 2 ℓ/day. Turnbull and Rodricks (1985) have cautioned that using rodent data to estimate di(-2-ethylhexyl) phthalate-promoted carcinogenic risk to humans may overestimate the actual risk. This caution was based on several factors including differences between rodents and primates in the metabolism of di(2-ethylhexyl) phthalate, a nonlinear relationship between the administered dose of di(2-ethylhexyl) phthalate and the dose of the hypothesized "proximate carcinogenic species" in rodents, the fact that the hypothesized "proximate carcinogenic species" is produced to a greater extent in rodents than in primates and differences in target site sensitivities between humans and rodents for liver tumors in general. These factors have not been evaluated as yet by EPA to see if an alternate risk assessment approach is warranted. Until such an analysis is conducted the q_1* should be considered to be an interim value.

8.2. DIETHYL PHTHALATE

U.S. EPA (1980b) derived an RfD of 13 mg/kg/day for diethyl phthalate. This value was based on a chronic oral rat NOEL of 1250 mg/kg/day (2.5% diet) defined by Food Research Laboratories (1955) and an uncertainty factor of 100. Higher doses (5% diet) caused a reduction in body weight. A reproduction study by Reel et al. (1984) demonstrated that F_1 but not parental mice exposed to 2.5% diethyl phthalate in the diet had fewer pups/litter, increased liver weights (males and females), increased prostate weights, decreased sperm concentration and increased pituitary weight (females only) in comparison with controls. Assuming that mice consume 13% of their weight in food/day, 2.5% is equivalent to 3250 mg/kg/day, a value well above the NOEL used to derive the RfD. Diethyl phthalate did not cause testicular atrophy in rats (Gray and Butterworth, 1980; Foster et al., 1980).

Although in general it is preferable to utilize chronic data over subchronic data for RfD development, deficiencies in reporting of the Food Research study reduce confidence in the data. Therefore, based upon a reevaluation of the two studies, the subchronic study of Brown et al. (1978) is chosen as the basis of the RfD. This study defined a NOAEL of 750 mg/kg/day with decreased body weight and increased liver weight seen at the next highest exposure level. Applying an uncertainty factor of 1000 (10 for subchronic to chronic, 10 for interspecies variability and 10 for interindividual variability) results in an RfD of 0.75 mg/kg/day, or 52.5 mg/day for a 70 kg human.

8.3. DI-n-BUTYL PHTHALATE

U.S. EPA (1980b) derived an RfD of 1.3 mg/kg/day based on a 52-week oral rat NOAEL of 125 mg/kg/day (Smith, 1953) and an uncertainty factor of 100. A higher dose (1.25% diet or 625 mg/kg/day) caused 50% mortality within 1 week of the initial exposure (Smith, 1953). A re-evaluation of this study suggests that the duration was not truly chronic and suffered from deficiencies of limited numbers of animals of a single sex. These factors suggest the application of an additional uncertainty factor of 10. The resulting RfD estimate is 0.125 mg/kg/day (8.75 mg/day for a 70 kg human).

Onda et al. (1974) observed the formation of renal cysts in the F_1 and F_2 generations of JCL and ICR mice exposed orally to either 10 or 100 mg/kg/day for three generations. These doses are below the NOAEL used by U.S. EPA (1980a) to derive the RfD for di-n-butyl phthalate. Since no details of the Onda et al. (1974) study were reported, it was not considered in risk assessment.

When di-n-butyl phthalate (0.12 or 0.6 g/kg/day) was administered to rats by gavage during gestation, an increased number of resorptions and reduced fetal body weight were observed at the 0.6 g/kg dose (Nikonorow et al., 1973). No gross skeletal effects were observed. Maternal toxicity was not reported, but significantly reduced placental weights were observed at both doses. Since there were no effects on reproductive or fetal endpoints in rats exposed to 0.12 g/kg/day, the reduced placental weight probably represents a NOAEL. The LOAEL for this study (0.6 g/kg/day) is well above the NOAEL used to derive the RfD.

Shiota et al. (1980) and Shiota and Nishimura (1982) observed maternal toxicity, fetotoxicity and gross external malformations in ICR mice fed 1% di-n-butyl phthalate in the diet (2100 mg/kg/day, as provided by the investigators) on days 0-18 of gestation. Significantly reduced numbers of ossified coccygia were observed at all levels of treatment (80, 180, 370 or 660 mg/kg/day), but there were no significant differences between controls and treated mice in incidences of skeletal malformations, lumbar rib variations or delayed sternal ossification. Doses ≤660 mg/kg/day would therefore represent NOAELs for this study and 2100 mg/kg/day represents an FEL. Di-n-butyl phthalate has been shown to cause testicular atrophy in rats, but only at doses greater than the NOAEL (125 mg/kg/day) used to derive the RfD (Cater et al., 1976, 1977; Gray et al., 1982; Gray and Butterworth, 1980). The RfD of 0.125 mg/kg/day is therefore recommended for ingestion of di-n-butyl phthalate.

8.4. DIMETHYL PHTHALATE

U.S. EPA (1980b) derived an RfD of 10 mg/kg/day for dimethyl phthalate based on a chronic rat NOEL of 1000 mg/kg/day and an uncertainty factor of 100. Higher doses caused chronic nephritis and decreased growth rate (Lehman, 1955). There are no other chronic oral studies for dimethyl phthalate. No adverse effects upon reproduction, growth or survival of offspring were observed in mice gavaged with dimethyl phthalate (3500 mg/kg) on days 7-15 of gestation (Booth et al., 1983; Plasterer et al., 1985). The pups were not examined for malformations. Furthermore, testicular effects were not observed in rats gavaged with dimethyl phthalate at doses equimolar to those at which di(2-ethylhexyl) phthalate caused testicular atrophy in rats (Gray and Butterworth, 1980; Foster et al., 1980). A reevaluation of the Lehman (1959) study suggests that the data as reported, are inadequate for RfD development.

8.5. DI-n-OCTYL PHTHALATE

The only available chronic study on di-n-octyl phthalate was reported in an abstract by Piekacz (1971), in which Wistar rats were given either 0 or 3500 ppm di-n-octyl phthalate in the diet for 7-12 months. Assuming that a rat consumes 5% of its weight in food/day, 3500 ppm is equivalent to a dose of 175 mg/kg/day. Females had elevated kidney and liver weights, and both males and females had increased SGOT and SGPT. Di-n-octyl phthalate did not cause testicular atrophy in rats when given orally at a dose equimolar to that at which di(2-ethylhexyl) phthalate caused testicular atrophy in rats (Gray and Butterworth, 1980; Foster et al., 1980). Furthermore, adverse effects on reproduction and fertility were not observed in 2 generations of CD-1 mice fed 1.25, 2.5 or 5% (12,500-50,000 ppm) di-n-octyl phthalate in the diet (Gulati et al., 1985).

The data base for di-n-octyl phthalate is limited and does not define a NOAEL, but the LOAEL of 3500 ppm (175 mg/kg/day) could be used to derive a provisional RfD. However, because of lack of details of data reporting, an RfD is not derived at this time.

8.6. n-BUTYL BENZYL PHTHALATE

n-Butyl benzyl phthalate has been tested for oncogenicity in feeding studies on F344 rats and B6C3F1 mice conducted by NTP (1982a). Statistically significant increases in the incidences of mononuclear cell leukemia and leukemia or lymphoma were observed in female rats. Because of the normally high background incidence of myelomonocytic leukemia in F344 rats, and because dose-related and significant decreases in malignant lymphoma, all lymphoma, and leukemia or lymphoma were observed in male mice in the same study, there is insufficient evidence to conclude that n-butyl benzyl phthalate is carcinogenic. IARC (1982a) concluded that the NTP (1982a) studies are insufficient to assess the carcinogenic potential of n-butyl benzyl phthalate. The equivalent EPA weight-of-evidence classification for this compound is Group C meaning that there is limited animal data and that the compound is considered a possible human carcinogen. It is therefore not appropriate to derive a q_1^* for n-butyl benzyl phthalate until further testing is performed.

Increased mortality caused by unexplained hemorrhaging was observed in male F344 rats fed 6000 or 12,000 ppm (300 or 600 mg/kg/day, using a food factor of 0.05) n-butyl benzyl phthalate (NTP, 1982a). The study was terminated after 28 weeks. In 90-day feeding studies on rats conducted by Monsanto (1972), rats were fed 0, 0.25, 0.5, 1.0, 1.5 or 2% (0, 125, 250, 500, 750 or 1000 mg/kg/day) n-butyl benzyl phthalate, and dogs were fed 0, 1, 2 or 5% (0, 250, 500 or 1250 mg/kg/day) n-butyl benzyl phthalate. No adverse effects were observed among dogs fed n-butyl benzyl phthalate at any level, or among rats fed 125 or 250 mg/kg/day n-butyl benzyl phthalate. Increased liver weights without accompanying histopathological changes were observed among rats fed 500-1000 mg/kg/day n-butyl benzyl phthalate.

Dietary concentrations of 2.5 or 5% have been shown to cause testicular atrophy in a 14-day study on rats (Agarwal et al., 1985).

In the NTP (1985) study, rats were fed dietary levels of 0, 0.03, 0.09, 0.28 and 0.83% butyl benzyl phthalate. Using data presented in the report, these dietary levels correspond to ~0, 17, 51, 159 and 470 mg/kg/day. At 2.5%, weight gain was significantly depressed and testicular and kidney lesions were apparent. In addition, liver-to-body weight ratios were increased and hematological evaluations suggested a pattern of increased erythrocyte turnover. At 0.83%, the only effects noted were increased absolute liver weight, increased liver-to-body weight and liver-to-brain weight ratios and increases in mean corpuscular hemoglobin.

Using the NOEL of 159 mg/kg/day (0.28%) and applying an uncertainty factor of 1000, an RfD of 11.1 mg/day could be developed; however, this value would not be protective for potential carcinogenic effects of this compound.

8.7. DIISONONYL PHTHALATE

The database for diisononyl phthalate is restricted to unpublished studies conducted by Livingston (1971) and reported in Krauskopf (1973). Dogs were dosed orally (method not specified) to 0, 0.125, 0.5% or a TWA of 2.8% (0, 31.25, 125 or 700 mg/kg/day using a food factor of 0.025) diisononyl phthalate for 13 weeks, with apparently only one dog/level of treatment. Rats were exposed orally to 0, 50, 150 or 500 mg/kg/day for 13 weeks. A slight reduction in growth rate and increased liver weight (absolute or relative not specified) were observed in high-dose rats. No effects were reported for rats treated with 50 or 150 mg/kg/day diisononyl phthalate. The dog treated with a TWA of 2.8% (700 mg/kg/day) diisononyl phthalate had decreased body weight, increased liver weight and histological changes in the liver, gall bladder and spleen. The dog given 0.5% (125 mg/kg/day) diisononyl phthalate had increased liver weight; no effects were observed at 0.125% (31.25 mg/kg/day). This report is considered inadequate for RfD development.

8.8. SUMMARY

An interim q_1^* of 8.36×10^{-3} $(mg/kg/day)^{-1}$ was derived for di(2-ethylhexyl) phthalate based on the incidence of hepatocellular carcinoma or adenoma in male mice in the NTP (1982b) study. The concentrations in water associated with risk levels of 10^{-5}, 10^{-6} and 10^{-7} are 4.19×10^{-2}, 4.19×10^{-3} and 4.19×10^{-4} mg/ℓ, assuming that a 70 kg human consumes 2 ℓ/day.

An RfD of 0.75 mg/kg/day (52.5 mg/day) for diethyl phthalate, was derived based on a chronic oral rat NOEL of 750 mg/kg/day in the study by Brown et al. (1978) and using an uncertainty factor of 1000. An RfD of 0.125 mg/kg/day (8.8 mg/day) for di-n-butyl phthalate was derived. The value is lower by a factor of 10 than that derived by U.S. EPA (1980b) based on a 52-week oral rat NOAEL of 125 mg/kg/ day in the study by Smith (1953). The difference is in the uncertainty factor with 1000. The U.S. EPA (1980b) derived an RfD of 10 mg/kg/day (700 mg/day) for dimethyl phthalate based on a chronic rat NOAEL of 1000 mg/kg/day in the study by Lehman (1955) using an uncertainty factor of 100. A reevaluation suggested that this report provides an inadequate basis for RfD development.

The only data available for di-n-octyl phthalate based on a subchronic rat LOAEL of 175 mg/kg/day in the study by Piekacz (1971) were considered inadequate for risk assessment. An RfD of 0.16 mg/kg/day (11.1 mg/day) was derived for n-butyl benzyl phthalate based on a subchronic rat NOEL of 159 mg/kg/day in the NTP (1985) study. An uncertainty factor of 1000 was used. It should be noted that butyl benzyl phthalate has been classified as an EPA Group C carcinogen. The proposed RfD would not necessarily be protective for potential carcinogenic effects. An RfD was not developed for diisononyl phthalate because of limited data.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

Oral studies have shown that di(2-ethylhexyl), di-n-butyl and di-n-heptyl phthalates can produce adverse effects upon the developing fetus when mice and rats are exposed during gestation (Wolkowski-Tyl, 1984a,b; Bell et al., 1979; Bell, 1980; Shiota and Mima, 1985; Shiota and Nishimura, 1982; Shiota et al., 1980; Nakamura et al., 1979; Yagi et al., 1978, 1980; Tomita et al., 1982b; Onda et al., 1974). These studies are summarized in Tables 5-4 and 5-5. Whether the observed effects (reduced fetal weight, fetal mortality, gross external and skeletal malformations) represent a primary effect of the compound in question or whether they occur as a result of maternal toxicity has yet to be demonstrated unequivocally. Studies conducted by NTP (Wolkowski-Tyl et al., 1984a,b) indicate that mice are more sensitive than rats.

Chronic or subchronic oral studies have been conducted with di(2-ethylhexyl), di-n-butyl, dimethyl, diisononyl, n-butyl benzyl and di-n-octyl phthalates (Carpenter et al., 1953; Harris et al., 1956; Nikonorow et al., 1973; Gray et al., 1977; Gangolli, 1982; NTP, 1982a,b; Kluwe et al., 1982b; Shaffer et al., 1945; Popp et al., 1985; Ganning et al., 1985; Nagasaki et al., 1974; Ota et al., 1974; Lake et al., 1976, 1977a; Maslenko, 1968; Food Research Laboratories, 1955; Brown et al., 1978; Smith, 1953; Lefaux, 1968; Piekacz, 1971; LeBreton, n.d.; Bornmann et al., 1956; Lehman, 1955; Livingston, 1971; Monsanto, 1972). Liver, kidneys and testes appear to be target organs. Relevant inhalation studies could not be located in the published literature as cited in the Appendix.

9.1.1. Di(2-ethylhexyl) Phthalate. Relevant chronic and subchronic data for di(2-ethylhexyl) phthalate are summarized in Table 5-7. The most severe effects occurring at the lowest dose were the teratogenic effects in the offspring of mouse dams treated by gavage with 91, 191 or 292 mg/kg/day on days 0-18 of gestation in the Wolkowski-Tyl et al. (1984b) study (see Table 5-4). These effects (external and visceral malformations and skeletal defects) occurred in the absence of signs of maternal toxicity at 91 mg/kg/day, warranting an RV_e of 10. The dose of 91 mg/kg/day (measured by investigators) was multiplied by the cube root of the ratio of mouse weight (0.029 kg; measured) to the reference human weight (70 kg) and by the human weight (70 kg) to obtain a human MED of 475 mg/day, which corresponds to an RV_d of 1.5. Multiplying the RV_e by the RV_d yields a CS of 15, corresponding to an RQ of 1000. Equivalent or less severe effects occurred at higher doses; therefore, calculation of a CS for these effects is not necessary. The only doses lower than 91 mg/kg/day at which effects occurred were 19 and 64 mg/kg/day, at which guinea pigs treated for 1 year had increased relative liver weights. The RV_e is 4. Multiplying the dose of 19 mg/kg/day by the cube root of the ratio of the reference guinea pig weight of 0.83 kg (Durkin, 1985) to the reference human body weight (70 kg) and by 70 kg results in an MED of 304 mg/day, which corresponds to an RV_d of 1.8. The CS is 7.2, which corresponds to an RQ of 1000.

9.1.2. **Diethyl Phthalate.** Toxicity data for diethyl phthalate are summarized in Table 5-8. The most severe effect is the reduced sperm concentration and reduced numbers of pups/litter in F_1 mice exposed to 2.5% diethyl phthalate in the diet (Reel et al., 1984). Assuming that a mouse consumes 13% of its weight in food/day, 2.5% is equivalent to a dose of 3250 mg/kg/day. Multiplying 3250 mg/kg/day by the cube root of the ratio of the reference mouse weight (0.03 kg) to human weight (70 kg), and by the human weight (70 kg) yields a human MED of 17,152 mg/day, which corresponds to an RV_d

of 1. An RV_e of 8 is assigned on the basis of reduced reproductive capacity. Multiplying the RV_e by the RV_d yields a CS of 8, which corresponds to an RQ of 1000. U.S. EPA (1983b) derived an RQ of 5000 based on the 2-year study by Food Research Laboratories (1955), in which rats had significantly reduced body weight gain (RV_e=4) at a dietary level of 5% (2500 mg/kg/day; MED=29,925 mg/day; RV_d=1). The CS is 4. The reproduction study of Reel et al. (1984) was not available during the preparation of the previous RQ document by U.S. EPA (1983b).

9.1.3. **Di-n-Butyl Phthalate.** Toxicity data are summarized in Table 5-9 and teratogenicity data are summarized in Table 5-5. The most severe effects were the fetotoxicity, teratogenicity and maternal toxicity in ICR mice exposed orally to 2100 mg di-n-butyl phthalate/kg/day (Shiota and Nishimura, 1982; Shiota et al., 1980). These effects warrant an RV_e of 9. Multiplying 2100 mg/kg/day by the product of the cube root of the ratio of mouse weight (0.03 kg; measured) to human weight (70 kg), and by the human weight (70 kg) yields a human MED of 11,083 mg/day, which corresponds to an RV_d of 1. Multiplying the RV_e by the RV_d yields a CS of 9, corresponding to an RQ of 1000.

Onda et al. (1974) apparently observed renal cysts in the F_1 and F_2 generations of rats treated orally with 10 or 100 mg di-n-butyl phthalate/kg/day for three generations. Since no details were provided, this study could not be considered in the derivation of an RQ.

Smith (1953) observed 50% mortality (5/10) within 1 week of daily exposure to 1.25% (625 mg/kg/day) di-n-butyl phthalate. This mortality may represent an acute response to a relatively high dose. Furthermore, the relevance of this finding to the derivation of an RQ is uncertain because the surviving rats gained weight as well as untreated controls, and did not exhibit pathologic or hematologic effects after 1 year of treatment (U.S. EPA, 1983a). Furthermore, using these data to derive a CS would not result in an RQ >1000 .

Shiota et al. (1980) and Shiota and Nishimura (1982) fed di-n-butyl phthalate to ICR mice on days 0-18 of gestation. In addition to the maternal toxicity, fetotoxicity and gross external malformations observed at 2100 mg/kg/day, there were significantly reduced numbers of ossified coccygia at all levels of treatment (80, 180, 370 or 660 mg/kg/day), but there were no significant differences between controls and treated mice in incidences of skeletal malformations, lumbar rib variations or delayed sternal ossification. In a previous RQ determination, U.S. EPA (1983a) used delayed ossification at 80 mg/kg/day as the basis for the RQ of 1000. An MED of 420 mg/day, an RV_d of 1.6 and an RV_e of 8 were calculated yielding a CS of 12.8 and an RQ of 1000. Nikonorow et al. (1973) treated rats with 600 mg/kg/day on days 0-21 of gestation and found reduced fetal body weight and increased numbers of resorptions (RV_e=8). Multiplying 600 mg/kg/day by the cube root of the rat weight (0.165 kg with study) to the human weight (70 kg) and by 70 kg results in an MED of 5590 mg/day, which corresponds to an RV_d of 1. The CS of 8 corresponds to an RQ of 1000.

In subchronic studies, Nikonorow et al. (1973) found increased liver weight without histological evidence of liver damage (RV_e=4) in rats treated with ≥120 mg/kg/day for 3 months; however, no treatment-related effects were observed in rats given 0.125% in the diet (62.5 mg/kg/day) for 1 year. Therefore, it is not necessary to divide the subchronic dose by an uncertainty factor of 10, because the resulting dose would be well below 62.5 mg/kg/day. Multiplying 120 mg/kg/day by the cube root of the reference rat weight (0.35 kg) to 70 kg, and by 70 kg, results in an MED of 1436 mg/day, corresponding to an RV_d of 1. The CS of 4 would correspond to an RQ of 5000.

Ota et al. (1974) observed marked degenerative changes in the liver and kidneys of mice given 500 or 5000 mg/kg/day for 3 months. This information was taken from an abstract, which provided little detail; therefore, this study was not considered for RQ derivation.

9.1.4. **Dimethyl Phthalate.** Toxicity data are summarized in Table 5-10. Lehman (1955) observed chronic nephritis (RV_e=7) in rats fed 8% dimethyl phthalate and decreased body weight (RV_e=4) in rats fed 4% dimethyl phthalate for 2 years. Assuming that a rat consumes 5% of its weight in food per day, 8% is equivalent to a dose of 4000 mg/kg/day and 4% is equivalent to 2000 mg/kg/day. Multiplying 2000 and 4000 mg/kg/day by the product of the cube root of the ratio of rat weight (0.35 kg; assumed) to human weight (70 kg; assumed), and human weight (70 kg) yields human MEDs of 23,940 and 47,879 mg/day, respectively. Both MEDs correspond to RV_ds of 1. Multiplying the RV_d by the RV_es of 4 and 7 yields CSs of 4 and 7, respectively, corresponding to RQs of 5000 and 1000, respectively.

9.1.5. **Di-n-Octyl Phthalate.** Only two chronic toxicity studies were available for the assessment of di-n-octyl phthalate (see Table 5-10); the 2-generation reproduction and fertility assessment conducted by Gulati et al. (1985) on CD-1 mice, and the 12-month toxicity study by Piekacz (1971) conducted on Wistar rats. No effects were observed by Gulati et al. (1985). A CS of 6 can be derived from Piekacz (1971) on the basis of elevated liver and kidney weights (female rats) and increased SGOT and SGPT (male and female) in rats fed 3500 ppm di-n-octyl phthalate. Assuming that a rat consumes 5% of its body weight in food per day, 3500 ppm is equivalent to a dose of 175 mg/kg/day. Multiplying 175 mg/kg/day by the cube root of the ratio of rat weight (0.35 kg; assumed) to human weight (70 kg; assumed) and human weight yields a human MED of 2095 mg/day. The MED is assigned an RV_d of 1. The RV_e of 6 is assigned on the basis of the above effects. Multiplying the RV_d by the RV_e yields a CS of 6. The RQ for di-n-octyl phthalate is therefore 1000.

9.1.6. **n-Butyl Benzyl Phthalate.** The toxicity data for n-butyl benzyl phthalate are summarized on Table 5-10. In a chronic dietary study, there was a dose-related and significant early mortality from unexplained hemorrhaging in male F-344 rats fed 6000 or 12,000 ppm n-butyl benzyl phthalate in the diet for 28 weeks (NTP, 1982a). In a subchronic study by Monsanto (1972), the only effect in rats treated for 90 days was increased liver weight at $\geq$10,000 ppm. Since the discrepancy cannot be resolved, a CS for the mortality is calculated. Assuming that a rat consumes 5% of its body weight in food per day, 6000 ppm is equivalent to 300 mg/kg/day. Multiplying 300 mg/kg/day by the cube root of the ratio of rat weight (0.375 kg in the study) to human weight (70 kg) and by the human weight (70 kg) yields a human dose of 3674 mg/day. Because the mortality occurred during 15-28 weeks, the dose should be divided by an uncertainty factor of 10. The resultant MED of 367 mg/day corresponds to an RV_d of 1.7. Multiplying the RV_d by the RV_e of 10 for mortality results in a CS of 17, which corresponds to an RQ of 1000.

9.1.7. **Diisononyl Phthalate.** The only studies available for the assessment of diisononyl phthalate are unpublished studies on dogs and rats conducted by Livingston (1971) and reported by Krauskopf (1973) (see Table 5-6). The RQ is based on slightly reduced growth rate and increased liver weight in rats treated with 500 mg diisononyl phthalate/kg/day for 13 weeks.

Dividing 500 mg/kg/day by 10 and multiplying by the cube root of the ratio of reference rat weight (0.35 kg) to the reference human weight (70 kg) and human weight (70 kg) yields a human MED of 598 mg/day. The MED corresponds to an RV_d of 1.3. An RV_e of 4 is assigned on the basis of the above effects. Multiplying the RV_e by the RV_d yields a CS of 5.2. The dog(s) given a TWA concentration of 2.8% had histologicaal changes in liver, gall bladder, spleen and kidney. Assuming that a dog consumes a daily amount of food equal to 2.5% of its body weight, the 2.8% concentration is equivalent to 700 mg/kg/day. Dividing by an uncertainty factor of 10 and multiplying by the cube root of the reference dog weight of 12.7 kg (Durkin, 1985) to the human weight, and by 70 kg, results in an MED of 2774 mg/day. The RV_d is 1, the RV_e is 6 and the CS is 6, which corresponds to an RQ of 1000.

9.1.8. Di-n-Heptyl Phthalate. The only available study of di-n-heptyl phthalate is the teratogenicity study by Nakashima et al. (1977), reported as an abstract (see Table 5-5). It is not appropriate to calculate a CS for this study, because, in the absence of other toxicity data, it is not known if fetotoxicity and teratogenicity are the most sensitive endpoints for this chemical. Furthermore, the data were not clearly presented.

9.1.9. Summary. CSs were calculated for di(2-ethylhexyl) phthalate, diethyl phthalate, di-n-butyl phthalate, dimethyl phthalate, di-n-octyl phthalate, n-butyl benzyl phthalate and diisononyl phthalate (Table 9-1). In each case, the data that resulted in the highest CS are recommended as the bases for the RQs (Tables 9-2 to 9-8). The RQ for each of the phthalate esters listed above is 1000. Data were not sufficient for deriving an RQ for the other phthalate esters discussed in this document.

TABLE 9-1

Summary of RQs Derived for Phthalic Acid Esters

Compound	Species (bw/kg)	Animal Dose (mg/kg/day)	Chronic Human MED (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
Diethylhexyl phthalate	guinea pig	19	305	1.8	Increased relative liver weight	4	7.2	1000	Carpenter et al., 1953
	mouse	91	475	1.5	Teratogenicity without maternal toxicity	10	15	1000	Wolkowski-Tyl et al., 1984b
Diethyl phthalate	rat	2500	29,925	1.0	Reduced body weight	4	4	5000	Food Research Lab., 1955
	mouse	3250	17,152	1.0	Decreased sperm concentration; reduced number of pups/litter in F_1	8	8	1000	Reel et al., 1984
Dibutyl phthalate	rat	600	5,590	1.0	Increased fetal resorptions; decreased fetal body weight	8	8	1000	Nikonorow et al., 1973
	rat	120	1,436	1.0	Increased liver weight	4	4	5000	Nikonorow et al., 1973
	mouse	2100	11,083	1.0	Fetotoxicity; teratogenicity; maternal toxicity	9	9	1000	Shiota and Nishimura, 1982; Shiota et al., 1980
	mouse	80	420	1.6	Fetotoxicity	8	12.8	1000	Shiota et al., 1980
Dimethyl phthalate	rat	4000	47,879	1.0	Chronic nephritis	7	7	1000	Lehman, 1955
	rat	2000	23,940	1.0	Decreased body weight	4	4	5000	Lehman, 1955
Dioctyl phthalate	rat	175	2,095	1.0	Elevated liver and kidney weights (F); increased SGOT and SGPT (male and female)	6	6	1000	Piekacz, 1971
n-Butyl benzyl phthalate	male rat	300	367*	1.7	Mortality due to unexplained hemorrhaging	10	17	1000	NTP, 1982a
Diisononyl phthalate	rat	500	598*	1.0	Slightly reduced growth rate; increased liver weight	4	4	5000	Livingston, 1971
	dog	700	2,774*	1.0	Histologic changes in liver, gallbladder, spleen and kidney	6	6	1000	Livingston, 1971

*The dose was divided by 10 to approximate chronic exposure

TABLE 9-2

Di(2-ethylhexyl) Phthalate

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose*:	305 mg/day
Effect:	teratogenicity without maternal toxicity
Reference:	Wolkowski-Tyl et al., 1984b
RV_d:	1.5
RV_e:	10
Composite Score:	15
RQ:	1000

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*Equivalent human dose

TABLE 9-3

Diethyl Phthalate

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose*:	17,152 mg/day
Effect:	reduced number of pups/litter; decreased sperm concentrations
Reference:	Reel et al., 1984
RV_d:	1
RV_e:	8
Composite Score:	8
RQ:	1000

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*Equivalent human dose

TABLE 9-4

Di-n-butyl Phthalate

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose*:	420 mg/day
Effect:	fetotoxicity
Reference:	Shiota et al., 1980
RV_d:	1.6
RV_e:	8
Composite Score:	12.8
RQ:	1000

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*Equivalent human dose

TABLE 9-5

Dimethyl Phthalate

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose*:	47,879 mg/day
Effect:	chronic nephritis
Reference:	Lehman, 1955
RV_d:	1
RV_e:	7
Composite Score:	7
RQ:	1000

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*Equivalent human dose

TABLE 9-6

Di-n-octyl Phthalate

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose*:	2095 mg/day
Effect:	elevated liver and kidney weights; increased SGOT and SGPT
Reference:	Piekacz, 1971
RV_d:	1
RV_e:	6
Composite Score:	6
RQ:	1000

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*Equivalent human dose

TABLE 9-7

n-Butyl Benzyl Phthalate

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose*:	367 mg/day
Effect:	mortality
Reference:	NTP, 1982a
RV_d:	1.7
RV_e:	10
Composite Score:	17
RQ:	1000

---

*Equivalent human dose

TABLE 9-8

Diisononyl Phthalate

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose*:	2774
Effect:	histologic changes in liver, gall bladder, spleen and kidney
Reference:	Livingston, 1971
RV_d:	1
RV_e:	6
Composite Score:	6
RQ:	1000

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*Equivalent human dose

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

9.2.1. Di(2-Ethylhexyl) Phthalate. In lifetime feeding studies conducted by NTP (1982b), di(2-ethylhexyl) phthalate was shown to cause increased incidences of liver neoplasms in F344/N rats (hepatocellular carcinoma, hepatocellular carcinoma or neoplastic nodules) and in B6C3F1 mice (hepatocellular carcinoma, hepatocellular carcinoma or adenoma). This study was discussed in detail in Section 5.1. and is summarized in Table 5-3. Based on these results, IARC (1982b) concluded that there is sufficient evidence that di(2-ethylhexyl) phthalate is carcinogenic for rats and mice. No human studies were available for evaluation. IARC has ranked di(2-ethylhexyl) phthalate as a group 2B compound. Using the EPA scheme, this compound can be classified as a B2 chemical (U.S. EPA, 1986b).

Since di(2-ethylhexyl) phthalate is probably carcinogenic for humans, it is appropriate to derive a potency factor. As discussed in Chapter 8, the highest q_1^*, a value of 8.36×10^{-3} $(mg/kg/day)^{-1}$ (interim value), was calculated from the data on increased incidence of hepatocellular carcinoma or adenoma in male mice; therefore, the same data are used in the calculation of F. The doses used in the multistage model were adjusted before the calculation of the q_1^* as follows:

$$\text{dose} \times le/L_E \times (W_A/70)^{1/3} \times (L_E/L)^3$$

where le = length of treatment study

L_E = length of study

W_A = animal body weight

L = lifespan of the animal; in this case $L=L_E$

In order to obtain a human $1/ED_{10}(F)$, adjustments for body weight and less-than-lifetime exposure are normally applied to the unadjusted animal $1/ED_{10}$ obtained from the computerized multistage model. However, since body weight varied in some of the dose groups in the NTP (1982b) study, these adjustments were applied to the doses before the calculation of $1/ED_{10}$. The resulting $1/ED_{10}$ is thus adjusted (human) F values (Table 9-9). Because the F factor of 5.14×10^{-2} $(mg/kg/day)^{-1}$ is <1, di(2-ethylhexyl) phthalate is placed in Potency Group 3. An EPA Group B2 chemical in Potency Group 3 has a low hazard ranking under CERCLA. The potency value is considered interim because there is evidence suggesting that metabolites may be responsible for the effects. EPA has not yet evaluated the possibility of utilizing metabolized dose as a means of accomplishing the interspecies conversion for the quantitative estimate. Until EPA evaluates the cancer data in the context of potential differences in metabolized dose the q_1^* should be viewed as an interim estimate.

Some dispute exists, however, concerning whether rodent studies on di(2-ethylhexyl) phthalate can be used to quantify potential effects in humans (Northrup et al., 1982; Kluwe et al., 1983; Turnbull and Rodricks, 1985). These doubts are based primarily on differences in the way di(2-ethylhexyl) phthalate is metabolized in rodents and humans, and hypotheses that the proximate carcinogenic species is produced to a greater extent in rodents than in humans (Turnbull and Rodricks, 1985) (see Section 5.1.). Turnbull and Rodricks (1985) suggest that human potency factors for di(2-ethylhexyl) phthalate that are based on rodent data probably overestimate the carcinogenic risk of di(2-ethylhexyl) phthalate for humans.

TABLE 9-9

Derivation of Potency Factor (F)
Agent: Di(2-ethylhexyl) Phthalate

Reference:	NTP, 1982b		
Exposure route:	Oral		
Species:	Mouse		
Strain:	B6C3F1		
Sex:	Male		
Vehicle or physical state:	Diet		
Body weight:	0.04 kg		
Duration of treatment:	103 weeks		
Duration of study:	105 weeks (low dose); 104 weeks (high dose)		
Lifespan of animal:	105 weeks (low dose); 104 weeks (high dose)		
Target organ:	Liver		
Tumor type:	Hepatocellular carcinoma or adenoma		
Experimental doses/ exposure (mℓ/kg):	0	3000	6000 ppm
	0	672	1325 mg/kg/day (measured)
Transformed doses* (mg/kg/day):	0	54.7	108.89
Tumor incidence:	14/50	25/48	29/50
Unadjusted $1/ED_{10}$:	Not calculated (see text)		
$1/ED_{10}$ (F factor):	5.14×10^{-2} (mg/kg/day)$^{-1}$		

*For all data from NTP (1982b), doses were transformed prior to calculation of $1/ED_{10}$ due to differences between treatment groups in body weight: dose x le/Le x $(0.04/70)^{1/3}$ x $(Le/L)^3$ = transformed dose, where Le/L = 1

9.2.2. n-Butyl Benzyl Phthalate. n-Butyl benzyl phthalate has also been tested for oncogenicity in feeding studies on F344/N rats and B6C3F1 mice conducted by NTP (1982a). These data are discussed in Section 5.1. and are summarized in Table 5-2. Based on the observation of increased incidences of mononuclear cell leukemia and leukemia or lymphoma in female rats, NTP (1982a) concluded that n-butyl benzyl phthalate was "probably carcinogenic for female F344/N rats." In a separate report, however, Kluwe et al. (1982a) concluded that since the background incidence of myelomonocytic leukemia is normally high in F344/N rats, results presented in NTP (1982a) provide only equivocal evidence of n-butyl benzyl phthalate-induced cancer in female rats. Furthermore, the fact that dose-related and significant decreases in malignant lymphoma, all lymphoma and leukemia or lymphoma were observed in male mice (NTP, 1982a) adds to the uncertainty that n-butyl benzyl phthalate may cause cancer in humans. IARC (1982a) concluded that the NTP (1982a) studies are insufficient to assess the carcinogenic potential of n-butyl benzyl phthalate.

Based on the normally high background incidence of leukemia in F344/N rats, on the compound-related decreases in leukemia and lymphomas in male B6C3F1 mice, and on interspecies differences in the metabolism of phthalates, the NTP (1982a) study provides only limited evidence of n-butyl benzyl phthalate-induced carcinogenicity. Therefore, n-butyl benzyl phthalate is best classified as an EPA Group C chemical, albeit with no potency factor derived.

9.2.3. Other Phthalate Esters. Other phthalate esters have not been tested for oncogenicity. These compounds are best classified in EPA Group D.

Phthalic Acid Esters

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CASR online (U.S. EPA Chemical Activities Status Report)
CAS online STN International
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in October, 1985. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

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Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

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Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

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Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

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